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THE RÔLE OF CLINICAL PATHOLOGY IN MEDICINE*

LORD HORDER

London, England

It would be invidious if I discriminated between the numerous invitations given to me, and the numerous acceptances cabled by me, in connection with my brief sojourn in the United States on this occasion. But if I had to choose that one which made the warmest appeal to me, I think it would be yours. In joining up with your group I am returning to an old love of, I regret to say, some more than thirty years ago. For of all the experiences I have had and of all the training I have received, none has been more satisfactory to me than those early years that I spent in going to and fro between the wards and the laboratory and the autopsy room, working at diagnostic and therapeutic problems whose solutions came through clinical pathological investigations. The spirit and the need of such methods, and a certain facility in the interpretation of the results obtained, have never left me in all my later work in the field of Clinical Medicine. You can perhaps understand, therefore, my pleasure in being among you and with what alacrity I replied to the letter from your president, Dr. Johns, whose tragic death we all so deeply deplore. All the more so that his invitation came through my friend and host, Dr. Sondern, himself a former president of your Society and a great pioneer in the field that you till with such success.

Your Society has existed just twice as long as the corresponding Society in Great Britain. As its first honorary member and as one who had the privilege of giving its inaugural address, I am glad that I have the happy duty of bringing you its greetings. Dr. Johns was good enough to mention, in his letter of invitation,

*Address read at the annual banquet held in honor of Dr. Frederick Sondern at the Fifteenth Annual Convention of the American Society of Clinical Pathologists held in Kansas City, June 8 to 10, 1936.

a little book which I had the temerity to publish as long ago as thirty years and called "Clinical Pathology in Practice." Perhaps it is just as well for medicine and for clinical pathology that it is long since out of print!

From a study of your program this morning, I gather that the range of your work is a good deal broader than is that of our sister association in England. This exists primarily to help the practicing physician and surgeon by mobilizing clinical pathologists for the purpose of discussing the principles, methods, and technic connected with the diagnosis and treatment of disease as viewed from their special angle. What I have to say this evening will bear, therefore, very closely upon this particular sphere of work and upon the valuable contributions which can be made to the actual practice of medicine by the members of such an association. In our Society all the members are practising pathologists. Most of them, but not all, are connected with teaching institutions and the professorial element is almost, if not completely, absent.

In England some doubts had been expressed in certain quarters as to the need for such an association. But in my own mind there could be no doubts. In every branch of medicine there is an academic and a practical side. In anatomy, in physiology, in physics, in biochemistry, men are working out special problems of an academic kind whose bearing upon the diagnosis and treatment of disease are only indirect. This is so in pathology also. But the doctor in charge of a patient would get very little help in the conduct of his case if he were dependent upon the activities of pathologists who are engaged upon abstruse problems. There needs special acquaintance with the actual manifestations of disease-processes, and experience in handling material derived from the patient, in order to supply important information which supplements the clinical features and makes it the whole, rather than a part, of the picture. Here, too, time is the essence of the contract. Pure research may be followed leisurely; indeed, to follow it any other way than deliberately and slowly invites failure. Clinical pathology demands promptness and concentration towards an immediate practical end; the individual's health,

perhaps life, is at stake. This puts a limit to contemplativeness and abstraction. It is the application of pathological principles to practical medicine, not the discovery of these principles themselves, that is the concern of clinical pathology.

To stress the importance of clinical pathology in medicine is no longer as necessary as it was years ago when pathology and clinical medicine were threatened by divorce. But even today it is still necessary to emphasize the importance of close association between pathologist and clinician. There is a unity in disease which demands a study of both aspects of the problem if the proper solution is to be found. If this be granted, then it is important that the pathologist gets as full a brief of the case from the clinician as is possible. In this matter the position is not too satisfactory. One fact which tends to obstruct this very necessary liaison is the existence of laboratories in which the personal link between doctor and pathologist is quite eliminated. Materials are dumped in these places much as coals are dumped at our houses. I suppose such places are necessary; anyway, they seem to have come to stay. I do not patronize them myself, because I am fortunate enough to be in frequent touch with colleagues working in hospital or private laboratories. But I am convinced that the commercializing of this part of our work is as bad for the patient and for us as it would be if clinical medicine (that is, doctoring in general) were itself commercialized. We are all so familiar with examples of the futility of pathological work and of conclusions drawn from it, when quite detached from the clinical features of the case, that to quote any of these would be superfluous. One bad effect of this detachment is a struggle to get farther by way of conclusion than the data supplied by the investigation admit. Too often the doctor tempts the pathologist to go beyond his facts but such temptation must be resisted. Often the particular investigation asked for is not pertinent and the pathologist can then give useful hints to the practitioner in this matter if he is consulted.

This reflection leads me to say a few words about clinico-pathological reports in general and the logic of them. In the first place it cannot be iterated too often that no amount of nega-

tive investigation ever establishes a positive result. But we often see this error made though the positive is veiled under the guise of a negative. To be more explicit, such a statement as this: "the infection is not in the typhoid-colon bacillus group" is equivalent to a categorical exclusion, which is not, of course, justified by the particular examination. What the pathologist really means is that, in the absence of specific agglutinations and a leukopenia and with no non-lactose fermenting coliform organisms obtained from the blood, urine, or feces, there is no evidence on his side of the inquiry of typhoid or paratyphoid fever. But the two methods of stating the same result are entirely different and the difference may mean that the doctor neglects a whole series of clinical facts which, taken together, make the diagnosis incontrovertible.

The final test in all cases is, of course, the patient and what happens to him. And it is only by maintaining a close liaison between pathologist and clinician that doubts can be settled and both parties be kept in the way of progress. We are familiar with the expression "pathology as an aid to clinical medicine." I was once bold enough to read a paper on "clinical medicine as a help to pathology."

The truth is, there are not enough consultations between clinicians and pathologists, and this applies both to hospital and to private practice.

Then there is the bedrock of the postmortem room. It is there that our vanity gets the shock that is so good for it and it is also there, I am glad to add, that our efforts get some of their best encouragement. (A statement which would read somewhat paradoxically to the layman.)

The prolixity of some pathological reports is very confusing to the practitioner. He often finds it difficult to distinguish between a mass of detailed technic and the conclusions pertinent to the case. "What does it all amount to" is a question I am sometimes asked, and I naturally refrain from answering, "precious little." It is occasionally hard to resist the conclusion that some reports seem to be written with a view of impressing the doctor with the thoroughness of the laboratory work that has been

done. When a method is used which has a differential value, this often finds a useful place in the report but technic which is merely of domestic interest may well be omitted.

There is another type of report which is apt to be unhelpful and likely to give the practitioner mental dyspepsia—that in which the essentials and the non-essentials are thrown together indiscriminately or in which certain findings, the significance of which is as yet unknown, are placed on a par with others, the meaning of which is established. When such reports are edited, there is sometimes very little left, and this little may be negative in respect to the particular case.

The introduction of results obtained by the use of methods and technic peculiar to the pathologist himself is another source of confusion. When this is the case the fact should be clearly stated so that the doctor may know the position. But the utmost forbearance should be exercised in such matters. The proper place for the discussion and criticism of new technic, and the validity of the results obtained from it, is the academic body of pathologists and also, of course, the Society of Clinical Pathologists itself. It should not be submitted to the judgment of the man in general practice, who has little opportunity for knowing what tests are established and accepted and what are not. If such forbearance is not exercised, a worse result than misleading the doctor is prone to ensue and that is that the pathologist comes to believe that a frequent reference to his pet idea has really proved that his thesis has passed into the realm of established facts. He then weaves it into the routine of his laboratory work as though it were a generally accepted method. Some men seem almost a law unto themselves in these matters; so much so that I can often tell who is the author of a report when it is read to me because of the inclusion of one or more of these—at present unaccepted—criteria. This sort of thing and its adjustment is, as I have already suggested, an important part of the work of a Society such as this.

I am not suggesting that everybody should make either his technic, or the form of his report, follow the same stereotyped plan: that would be to stultify individual effort and individual

genius. There is a personal equation in these things as there is in all others and this is an element which, properly controlled, makes for progress. But I should like to plead for greater uniformity in methods, in nomenclature, and in the criteria to be generally accepted in clinical pathology. Much has already been done in this connection and by Societies like yours. Much, however, still remains to do.

Standardization in clinical pathology has been greatly helped by fuller and clearer instructions to the practitioner as to how to collect the necessary materials and how to forward them to the laboratory. Vessels and other media for transport have improved considerably. The whole thing is much more fool-proof than it formerly was. It cannot be made too fool-proof. Of course, it is far better that the pathologist should obtain his own specimens first hand and this should be encouraged whenever possible. Unfortunately, this ideal is frequently unattainable; distance and expense often make it prohibitive and I suppose distance is a greater obstacle here than it is in my country. All the more does it behoove the pathologist to be very explicit as to his needs and all the more necessary is it to supply the appropriate bottles, pipets, tubes, slides, and so forth. I have no doubt your Society has prepared a small and helpful booklet on these matters of collection and transport of materials and that it is in the hands of every doctor.

If I were to instance one field of investigation in which there is still need for greater uniformity of method it would be the feces. The divergent results so frequently seen in reports on the stools from the same case, for example, are largely due to the widely divergent conditions in which specimens are taken. In one instance a piece of mucus is carefully selected and forwarded promptly to the pathologist. In another, a fragment of dried-up material which has been a long time in transit is used for the same examination. The effect of an aperient upon the flora of the stool is often quite disregarded; so also is the diet.

There is still insufficient attention paid to the importance of a catheter specimen of the urine in a female when the investigation is a bacteriological one. Moreover, the doctor should be urged

to pass the catheter himself: too often the nurse adopts the stupid method of performing this little operation by touch and not by sight, which is "walking by faith" with a vengeance.

The importance of filming the sputa in acute respiratory diseases is not sufficiently stressed.

In dealing with biopsy, the instructions should be specially clear. In the case of lymph nodes the doctor, left to himself, too often tends to remove the node which is firmest in texture and most isolated. Such nodes may yield histological features that are residual, as for example, fibrosis and necrobiotic changes. Whereas a softer gland, perhaps one of a group, is more likely to show active and specific histological elements with, or without, positive bacteriological results. This adaptation of the material in regard to the chance of a positive finding is important in others than the tissues used for biopsy. It applies, for example, to sputa. To report the absence of tubercle bacilli in material that is merely saliva, or chiefly blood, has quite a different significance from a negative report obtained by the examination of a muco-purulent or caseous specimen. This is all very obvious to those of us who have been through the mill, but it is not always obvious to the practitioner and his attention may often usefully be drawn to such facts as these.

Turning, lastly, to the actual technics of laboratory work, here again Societies like this are invaluable in their efforts at effecting better standardization of methods. To speak once more of the feces, cannot more be done to make the cultural methods more uniform? The amount of confusion at present existing is very great, and when we add that the nomenclature is based upon different principles, it follows that thousands of reports are quite equivocal. The doctor has come to consider that a bacteriological examination of the stools is desirable: the patient thinks it ought to be done: but there the matter ends. There is the question of dilution, upon which quantitative results almost entirely depend. There is the question of the culture media used. There is the question of the time allowed for culture. Lastly, there is the question, admittedly a vexed one, of the criteria of pathogenicity. I am, of course, aware that in the present state of

our knowledge of both the coliform and the streptococcal groups, some of the results must necessarily be tentative. But it seems to me to be far better and more helpful, during this period of half-knowledge, that the report should only record data which are co-related to established facts than that they should include debatable matters. Let me mention two instances, both of them having to do with pathogenicity. There is the question of "late lactose fermenters." *How* late seems to be a pertinent point, and this is frequently omitted. If we are not yet in possession of enough facts to justify us in formulating a group of coliform bacilli of certain pathogenic value under this heading, an explanatory note to this effect should be added when reference is made to their presence. Then I see reports in which the term "serum resisting coliform organisms" is used. But the connotation of the term is usually left open to the imagination of the practitioner. I could, as you know, easily multiply these examples.

I must not weary you further nor do I presume to give you either advice or warning. Let me rather conclude by expressing a hope that with all your splendid activities in the direction of improving technic and your interesting excursions into pure pathology, you will bear in mind the peculiar needs of your colleagues who are in charge at the bedside and demonstrate to them through practical help how great a contribution the laboratory can make the clinical medicine.

THE DIAGNOSTIC VALUE OF THE FREI REACTION IN LYMPHOGRANULOMA INGUINALE*†

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According to present knowledge, lymphogranuloma inguinale is an infectious disease caused by a filtrable virus with lymphotropic tendencies (Levaditi and coworkers; Hellerstroem and Wassen). Its importance as a venereal infection has recently been stressed by such authorities as Chevallier, Gaston, Loehe and Kerl, and in an investigation by the International Bureau of Public Health of the League of Nations Nicolau and others emphasize the marked increase of the disease during the past decade.

Two years of intensive study has proved that lymphogranuloma inguinale is widespread amongst the negro population of New Orleans and the surrounding rural districts, and we have been able to observe during that period 547 cases of the disease in its various clinical manifestations. As emphasized in our previous communications, the great variety of lesions caused by the virus in both sexes and the striking similarity of some of these lesions to the manifestations of other venereal diseases, especially syphilis, make the clinical diagnosis of lymphogranuloma inguinale extremely difficult and sometimes even impossible. Those circumstances are largely responsible for the disease remaining unrecognized for a number of years, although a review of hospital charts of twenty years ago suggests its presence in New Orleans at that time (von Haam, Lichtenstein).

More reliable as a diagnostic means than the clinical picture are the pathological lesions of the disease, described so excellently

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by Durand, Nicolas and Favre and found to consist essentially of an inflammatory reaction of the regional lymph glands and lymph vessels with the formation of small multiple abscesses and resulting chronic lymphstasis, followed ultimately by elephantiasis and fibrosis of the affected tissue. However, the frequent presence of secondary infectious processes and the equally frequent combination of lymphogranuloma inguinale with other venereal diseases such as chancroidal infections, veils the characteristic pathological picture often to such an extent as to render the diagnosis from biopsy or necropsy material impossible. The same circumstances may make demonstration of the causal filtrable agent by means of animal experiments extremely difficult. So can it be explained that until recent years the diagnosis of the disease has been made only in comparatively few cases.

The introduction of the specific skin test by Frei in 1925 can rightly be hailed as a "milestone of great importance" (Stannus) in the diagnosis of lymphogranuloma inguinale and has stimulated tremendously further studies of the disease. With the aid of this test, the etiological relationship between lymphogranuloma and climatic bubo (Findlay), inflammatory stricture of the rectum (Frei and Koppel), nonspecific urethritis of Waelsch type (Frei, Wiese and Klestadt), etcetera, can be demonstrated, and the complete clinical entity of this virus disease was ultimately established. The antigen used by Frei consisted of diluted and heated pus aspirated under sterile precautions from acute fluctuating bubos. Heated emulsions of excised bubos ground in saline solution (Dind) give an equally satisfactory antigen. The absolute specificity of this test has been defended by Frei in numerous publications and has been confirmed by numerous workers in all parts of the world. Since the condition of allergy which is the cause of the positive skin reaction remains for many years after healing of the lesions—perhaps even throughout the life of the patient—a positive reaction does not indicate the presence of the active disease and has perhaps less differential diagnostic value than a negative reaction, which definitely excludes the infection, either active or latent. This fact must be borne in mind especially in positive reactions obtained in older individuals in whom

the possibility of a previous infection with lymphogranuloma inguinale should always be excluded by careful consideration of the past history. On the other hand, some time must elapse after infection before the specific allergic state of the organism is reached; therefore, false negative reactions are frequently encountered, especially in very acute cases and in persons with slow allergic responses. These factors explain the majority of discrepancies which have been reported between the clinical findings and the results of the Frei test. Careful evaluation of clinical history and repetition of the test after a lapse of some time will clear most such apparent discrepancies and considerably increase the diagnostic value of the Frei test. Faulty technic in the preparation of the antigen is undoubtedly a frequent cause of faulty reactions. The antigen must be prepared from material obtained from a typical case of the disease, and its sterility should be tested repeatedly. Control reactions should always be performed in order to exclude false positives resulting from general skin hypersensitivity. Hellerstroem also stresses the fact that the true reaction appears "delayed", that is, after 48 hours, as a good criterion for its differentiation from pseudo reactions.

In our laboratories, the intracutaneous reaction of Frei has been used extensively and has proved an excellent method for the diagnosis of lymphogranuloma inguinale in its various manifestations. Our confidence in the reliability of this test has been justified by numerous cases in which animal inoculation confirmed the results of the Frei test while the clinical and biopsy diagnoses failed to reveal the true nature of the condition. During the last two years, we have performed over 1,600 Frei tests on patients with or without lymphogranuloma inguinale and wish to present our impressions of the diagnostic value of the test.

In the latter part of 1933, we encountered during the examination of tissues removed at operation material from a case of vulval elephantiasis which histologically met the criteria established for lymphogranuloma inguinale. We reported the case as such, and our interest being aroused, decided to investigate the possible occurrence of the disease in our locality. Our next case of lymphogranuloma inguinale was diagnosed during the spring of 1934

with antigen obtained through the kindness of Dr. Cole of Cleveland. From this case we prepared our own antigen for future diagnostic studies.

PREPARATION OF ANTIGEN AND TECHNIC OF THE FREI TEST

At first we used antigen prepared from the pus of bubos according to Frei's directions. Later we adopted Dind's method of preparing antigen from heated emulsions of excised glands, ground in saline solution and diluted to 10 per cent by weight. By this method, a more potent antigen was obtained.

Although both types of human antigen proved satisfactory, we found difficulty in standardizing the various batches of antigen obtained from material secured from various patients. Pus obtained from some cases proved to possess much weaker antigenic properties than that from other cases, and although we pooled the various antigens obtained over a certain period, their individual

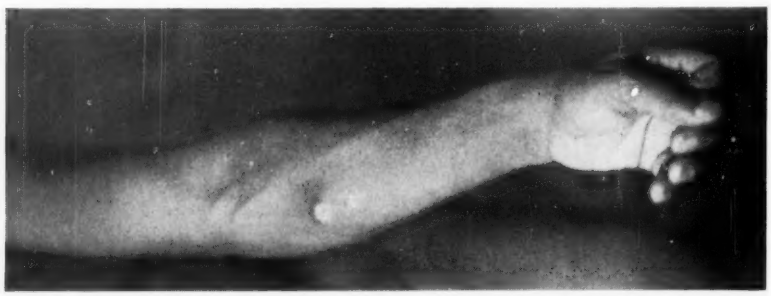

FIG. 1. FREI TEST ON CASE OF ACUTE BILATERAL INGUINALE BUBO WITH POSITIVE REACTION AND BARELY VISIBLE CONTROL

differences seemed to influence the appearances of the reactions. We therefore adopted brain emulsions of animals experimentally infected with the disease as standard antigen and this antigen prepared routinely in our laboratories has proved the method of choice in obtaining acceptable results over a long period. While numerous animals are susceptible to the disease, only the brain emulsions of infected monkeys (common marmoset or *Hepale penicillata*) and white mice have proved useful as antigen material. Since purchase of this type of monkey in the United States is difficult, we finally adopted the white mouse as the standard animal for antigen production.

Since our clinical experience suggested the possibility of virus strains of various virulences in different patients, we chose from forty strains carried in our laboratories for from four to twenty-six animal passages, the six which produced the strongest reactions in animals as a source of antigen production. These six strains (numbers 21, 24, 39, 40, 41 and 68) are carried through mice by biweekly

intracerebral injections and have remained unchanged in power of invasiveness for these animals. The inoculated dose is such that at the end of two weeks the infected animals show signs of sickness with marked histopathological

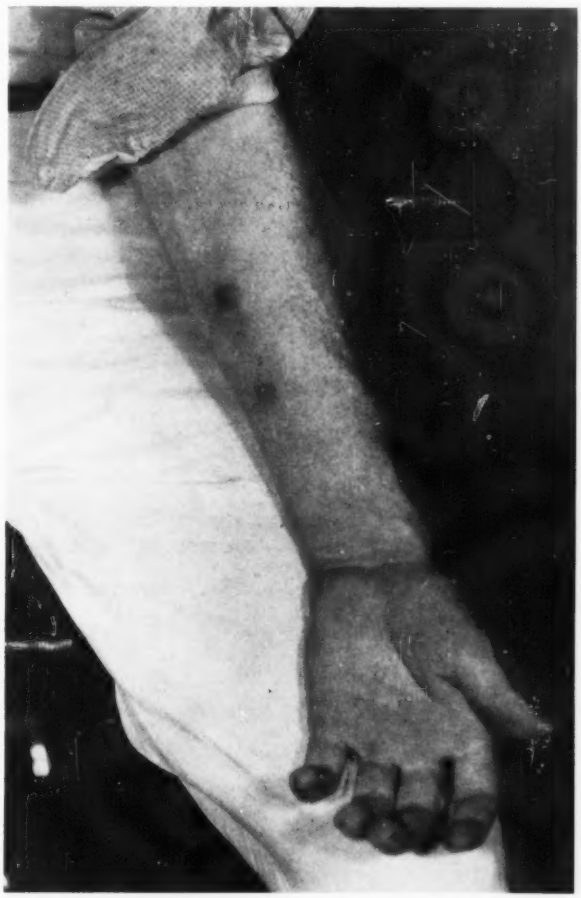

FIG. 2. POSITIVE FREI REACTION IN A WHITE PATIENT

The proximal reaction was produced by standardized polyvalent mouse antigen, the distal reaction by antigen prepared from human glands.

changes in their brain and meninges, but only few die. Preparation of antigen from the brains of these animals follows the general outline published by Frei and Hellerstroem (Lichtenstein and von Haam). A 10 per cent emulsion of brain in saline solution is heated at 60°C. for two hours the first day and for

one hour the second day. Five tenths per cent phenol is used as a preservative and repeated sterility tests are performed in order to avoid using infected material. Antigens prepared from the various strains are pooled, the stock mixture containing all six strains. Stock antigen is kept in the ice box (4°C.) in the dark and the "date of expiration" empirically set at six months. Samples of older batches are always available for control tests. Before being used for diagnostic purposes, each batch of mixed stock antigen is tested for specificity and sensitivity. At least six tests on known cases of lymphogranuloma ingui-

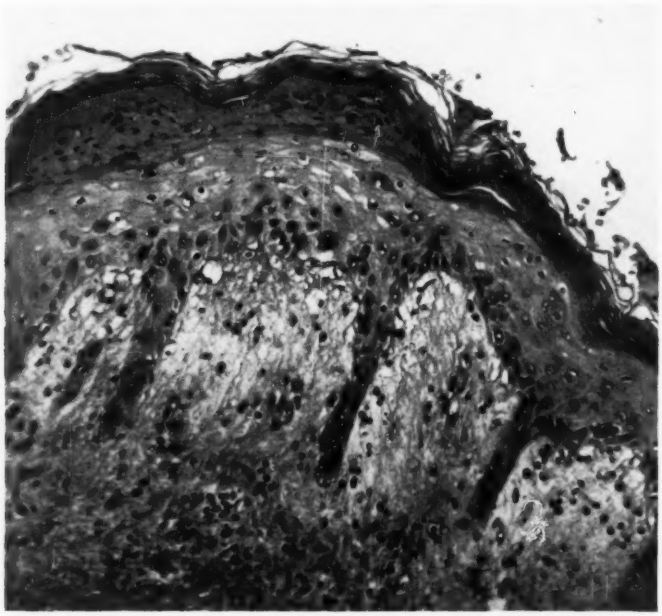

FIG. 3. MICROSCOPIC SECTION OF SKIN WITH POSITIVE FREI TEST

Marked epithelial and subepithelial edema; deep seated cellular reaction. (Hematoxylin-eosin, ×120.)

nale and six control tests on negative patients are performed and the results compared with those obtained with other stock antigen mixtures and human antigens. By these means we have succeeded in obtaining an antigen of high specificity and sensitivity which always produces the same type of reaction when tested on the same patients under similar conditions.

The technic of the Frei test we employ follows in general the directions given by Frei. After cleansing the forearm with alcohol, 0.1 cc. of the antigen is injected intradermally through a fine needle, a small weal of from 3 to 5 millimeters in diameter being produced. On the same arm the same quantity of

normal brain emulsion from healthy white mice prepared and treated in the same manner and of the same age as the antigen emulsion is similarly injected as a control. The use of mouse brain emulsion as control for the antigen prepared from mouse brain is absolutely necessary and preferable to any other control injection. The reaction is read after 48 hours and reported as doubtful, positive, strongly positive or negative. Doubtful reactions are not regarded as diagnostic and are repeated. If possible a second reading is made on all reactions after four days. The site of the control injection at the time of the reading

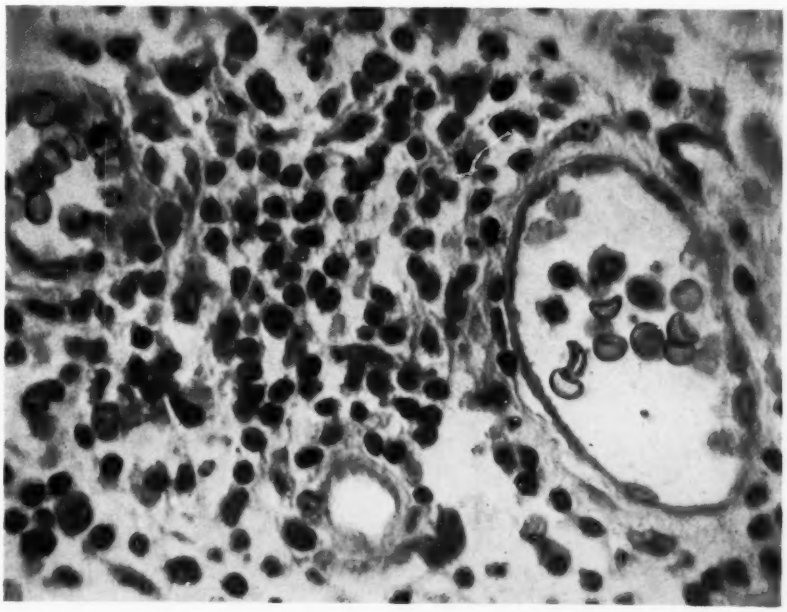

FIG. 4. SECTION THROUGH SUBCUTANEOUS TISSUE IN POSITIVE FREI REACTION

The inflammatory exudate consists principally of small round cells. (Giemsa stain, ×450.)

of the reaction usually shows only the mark of the needle puncture, with sometimes, a small deposit of unabsorbed material (fig. 1). The positive reaction consists of an elevated and inflammed weal, 0.5 cm. to 1 cm. in diameter. The strongly positive reactions show a red, edematous area measuring several centimeters in diameter, and usually containing centrally placed small yellowish areas of necrosis (fig. 2). The positive reactions are discernible for several days and sometimes heal with distinct pigmentation at the area of injection. The microscopic lesion produced by the positive Frei reaction shows marked hy-

peremia with vascular dilatation and perivascular accumulation of lymphocytes and plasma cells with comparatively few neutrophiles. The epithelium shows some edema but ordinarily no other evidence of damage. In the severe reactions necrosis including even the subdermal tissue is not uncommon. We have not been able to demonstrate inclusion bodies or ordinary bacteria in the lesions (figs. 3 and 4).

ANALYSIS OF RESULTS

Table 1 shows the number of positive, doubtful and negative reactions in cases clinically diagnosed as lymphogranuloma inguinale and in new cases consecutively admitted for varying conditions. In 547 cases in which the clinical, and in a large number the biopsy diagnosis, was lymphogranuloma inguinale, positive Frei reactions were obtained in 91.3 per cent or 499 cases.

TABLE 1

REVIEW OF 1,679 FREI REACTIONS

RESULTS OF FREI TESTS	SERIES A TESTS MADE ON CLINICAL CASES OF LYMPHOGRANULOMA INGUINALE TOTAL NUMBER 547	SERIES B TESTS MADE ON NEGRO PATIENTS SUFFERING FROM VARYING CONDITIONS TOTAL NUMBER 1,132
Positive	499 (91.3%)	197 (17.4%)
Doubtful	33 (6.0%)	39 (3.5%)
Negative	15 (2.7%)	896 (79.1%)

There were fifteen negatively reacting patients in this group of which seven remained negative on repeated tests, while eight deserted and could not be retested. Thirteen of these patients were colored males with acute inguinal bubos; two, females, had inflammatory strictures of the rectum. In thirty-three cases doubtful reactions were obtained, in nineteen even after repetition of the test. One thousand, four hundred sixty-nine patients who applied to the Hospital for a variety of conditions were Frei tested and 1,132 reactions on these were read, the others not returning to the Hospital. In this series, 197 (17.4 per cent) positive reactions and 896 (79.1 per cent) negative reactions were obtained. Further analysis of the tests performed on these patients is given in table 2. Group I comprises all cases in whom

definite evidence of lymphogranuloma inguinale could be found. Five hundred sixty-four (90.8 per cent) of these gave a positive Frei reaction. Group II comprises all cases in whom the history was strongly suggestive of a previous infection with the virus, including cases with inguinal scars, nonspecific vaginal and cervical lesions, complaints of some rectal distress without definite stricture. Ninety-four (78.3 per cent) gave a positive Frei reaction. Group III includes cases in whom no definite history of previous infection could be elicited because of the poor memory or the low intelligence of the patients. Twenty-seven cases (3.9 per cent) of all positive Frei reactions fell in this group. Group IV is made up of cases in which there was a definite denial

TABLE 2

ANALYSIS OF 1,679 FREI REACTIONS

CLINICAL DIAGNOSIS	FREI REACTION POSITIVE	FREI REACTION DOUBTFUL	FREI REACTION NEGATIVE
I. Cases of proved lymphogranuloma inguinale	564	35	22
II. Cases strongly suggestive of lymphogranuloma inguinale	94	6	20
III. Cases uncertain for lymphogranuloma inguinale	27	19	869
IV. Cases negative for lymphogranuloma inguinale	11	12	

of any possible infection with lymphogranuloma inguinale. This group consisted mainly of persons of considerable intelligence or young children and neither careful history nor physical examination revealed any suspicion of present or past infection with lymphogranuloma inguinale. Eleven of these cases (1.3 per cent) gave positive reactions. Seventy-two reactions or 4.3 per cent of the grand total of 1,679 reactions proved doubtful. Most of these could not be repeated because of lack of coöperation on the part of the patients. Amongst the 911 patients reacting negatively, forty-two showed some clinical evidence of lymphogranuloma inguinale infection.

The interesting and much discussed coincidental occurrence of

other venereal infections during the course of lymphogranuloma inguinale has been investigated in our present study and our observations thereon are recorded in table 3. Syphilis, as diagnosed by a positive blood Wassermann, reaction was by far the most frequent concomitant venereal infection occurring in 20.2 per cent of the Frei positive cases of series A (proved cases of lymphogranuloma inguinale) and in 18.7 per cent of the Frei positive cases of series B (routine hospital patients). One hundred ninety-two patients of the Frei negative cases of series B (22 per cent) also had positive blood Wassermann reactions. None of the Frei positive cases showed acute manifestations of both infections so it is not possible for us to discuss the problem of the

TABLE 3

COINCIDENTAL VENEREAL INFECTIONS IN FREI POSITIVE CASES

TYPE OF VENERAL INFECTION	SERIES	NUMBER OF CASES WITH COINCIDENTAL INFECTION	POSITIVE CASES
			per cent
Syphilis diagnosed by the positive Wassermann reaction	A	101	20.2
	B	37	18.7
Gonorrhoea diagnosed by positive smear	A	46	9.2
Chancroid diagnosed by positive smear or Dmelco's reaction	A	40	8.0
Granuloma inguinale diagnosed by positive smear	A	6	1.2

simultaneous occurrence of acute syphilis and acute lymphogranuloma inguinale at this time. Gonorrhoeal infections, chancroids and granuloma venereum were only recorded when active stages of the disease with visible lesions were present and when appropriate laboratory tests disclosed their etiological agent.

From the standpoint of actual diagnostic technic table 4 is indeed interesting. It shows a comparison of the various antigens used in the cutaneous reactions. From these data it must be admitted that antigens prepared from the brains of infected mice and from diluted pus obtained from human lesions give a higher percentage of doubtful reactions than do those prepared from the brains of infected monkeys and from excised human glands. We

have been impressed throughout this investigation by the fact that antigens prepared from the brains of infected marmosets give the best diagnostic results, but were forced because of the technical difficulty in obtaining this species of monkeys to use mouse brain antigens.

We have used other diagnostic antigens. Antigen kindly sent us by Doctors Grace and Suskind gave results quite comparable with those obtained with our own. The serum antigen of Doctors Tamura and Foshay, which is said to produce a quick reaction has been proved valuable. Attempts to produce diagnostic febrile reactions by intravenous injection of small doses of antigen according to the method of Hellerstroem and Ravaut gave us irregular results and cannot on the basis of our experience be

TABLE 4

COMPARISON OF ANTIGENS

TYPE OF ANTIGEN	POSITIVE REACTIONS	DOUBTFUL REACTIONS	NEGATIVE REACTIONS	TOTAL
Human antigen prepared from diluted pus	54	9 (5.3%)	106	169
Human antigen prepared from excised glands	122	5 (1.5%)	252	379
Monkey brain antigen	163	10 (1.9%)	349	522
Mouse brain antigen	357	48 (7.8%)	204	609

recommended. The addition of convalescent serum to antigen material according to Reiss' method neither increased nor decreased the specificity or sensitivity of the Frei test. Classification of patients suffering from acute lymphogranuloma inguinale according to local and general symptoms in two groups as suggested by Coutts and his coworkers and depending also upon differing allergic response to different "strains" of the etiological agent was not possible in our series.

Table 5 summarizes both series of tests. One hundred fifty-two reactions or 9.6 per cent are in the group of doubtful or faulty reactions, while in only 33 reactions (1.9 per cent) truly incorrect results were obtained. In 1,527 cases (90.9 per cent) diagnosis based on the test proved to be correct.

In addition to our own experiences, we are able to record that of others in the use of our diagnostic antigen. At the meeting of the Southern Medical Association held as St. Louis, Missouri, in the fall of 1935, we distributed sample portions of our mouse brain antigen with directions for its use. Later we sent a questionnaire to the physicians so supplied seeking to learn their opinions of the test material. In table 6 a brief resume is given of the answers received from the 45 physicians we were able to contact up to the time of publication of this report. Twenty-one reported favorable results, stating that the reaction usually coin-

TABLE 5

SUMMARY

Positive Frei reactions in cases of lymphogranuloma inguinale	658	(90.9%)
Negative Frei reactions in negative control cases	869	
Doubtful reactions	119	(7.2%)
Faulty, negative Frei reactions in lymphogranuloma inguinale	22	(1.9%)
Faulty, positive Frei reactions in negative control cases	11	

TABLE 6

EXPERIENCE OF OTHER PHYSICIANS WITH THE FREI ANTIGEN

(Based on the use of sample ampules distributed at the Southern Medical Association convention, St. Louis, Missouri, fall, 1935)

	NUMBER OF COLLABORATING PHYSICIANS	POSITIVE REACTIONS	DOUBTFUL REACTIONS	NEGATIVE REACTIONS	FALSE REACTIONS
Satisfactory	21	78	9	48	
Unsatisfactory	5	6	7	11	31

cided with the suspected clinical diagnosis. Incidentally some of those reports came from states where the presence of lymphogranuloma inguinale has not as yet been reported. Five physicians reported unfavorable results and nineteen, mostly from the St. Louis area, reported that they had had no occasion to apply the test. Most interesting is the fact that two physicians reported "too many positive reactions" and "lack of specificity," while three reported "too many negative reactions," and a "lack of sensitivity." We believe the reports attest to the efficacy of our antigen and to the diagnostic value of the Frei test since men

untrained and inexperienced in applying and reading it obtained 83.3 per cent satisfactory results.

COMPARISON WITH SIMILAR REPORTS

While it is beyond the scope of this report to survey and comment on all instances in which the Frei reaction has been used, brief mention will be made of the recent reports of large series of cases in which the test was used. De Wolf and Van Cleve reported in 1932 the results of 1,227 Frei tests performed on colored and white patients. They obtained sixty-four positive reactions corresponding to an incidence of 5.2 per cent. All of their positive cases gave rather conclusive histories of active or healed infection with lymphogranuloma inguinale; six of these positive cases (10 per cent) suffered from a concomitant venereal disease. Flandin, Rabeau and Turiaf in 1935 reported 1,170 Frei reactions on 400 patients. They made use of monkey and human antigens and obtained in 97 per cent of cases a correct diagnosis. In their conclusions they stress the diagnostic value of the test. Clement-Simon, Braley and Mink applied the Frei test to fifty female patients picked at random and obtained 12 per cent positive results, while only one patient showed an esthiomene-like lesion on the vulva which could be considered clinically as evidence of infection with the virus. Their conclusion that the Frei reaction gives erroneous results in 10 per cent of cases tested is sharply criticized by Sezary who points to the possibility of a latent or veiled infection which is especially common in females. Fifteen cases of inguinal bubo tested by Galloway of the United States Navy Medical Corps in 1936 gave positive reactions, while fifteen control cases were negative. In an interesting report Strauss and Howard (1936) claim that antigens prepared from brains of infected mice give false positive reactions some time after their preparation as will antigens prepared from brains of normal mice. Their results are at marked variance with our experiences and we are at a loss to explain them. Strauss and Howard make no mention as to how their antigens were stored or preserved, nor as to their sterility, all important factors as we have previously stressed. Since their report, we have performed a series of Frei

tests using mouse and human antigens eight months old and still obtained diagnostically correct reactions. We have encountered hypersensitivity to normal mouse brain and monkey brain emulsions, and it is for this reason that we insist upon homologous antigen controls in all tests.

SUMMARY AND CONCLUSIONS

The results of the Frei test in 547 cases of clinical lymphogranuloma inguinale and 1,132 negro hospital patients suffering from various conditions are reported. In 90.9 per cent of the cases diagnosis based upon the test proved correct; 7.2 per cent doubtful reactions were obtained; in 1.9 per cent of the cases apparently faulty reactions occurred.

Syphilis as indicated by positive blood Wassermann reactions was present in 19.5 per cent of Frei positive cases and in 22 per cent of Frei negative cases. Acute gonorrhoeal and chancroidal infections were present in about 10 per cent of the Frei positive cases.

Comparison of the various antigens used for the Frei test showed that antigen prepared from human gland and brain emulsions of experimentally infected marmosets give fewer doubtful reactions than do antigens prepared from diluted pus of human lesions and brain emulsions of infected mice.

These results of 1,697 Frei tests performed in our laboratories during the last two years demonstrate the marked degree of specificity and the high diagnostic value of this cutaneous reaction in the recognition of lymphogranuloma inguinale in its various manifestations. The fact that 17.4 per cent of negro patients applying for varying conditions to the Charity Hospital of Louisiana at New Orleans gave a positive reaction demonstrates the wide distribution of the disease amongst the members of that race in New Orleans and vicinity.

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SIMPLE SLIDE AND TUBE TESTS FOR INFECTIOUS MONONUCLEOSIS

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The blood picture in infectious mononucleosis, and the other clinical findings as well, are in themselves not entirely specific nor typical and there is often great difficulty in positive or differential diagnosis, especially from early lymphatic leukemia. Further aid in the diagnosis is offered by a heterophile antibody test that appears to be specific for the disease as pointed out by Paul and Bunnell[11], using the technic of agglutination employed by Davidsohn[6]. Two modifications of that procedure that have the advantage of greater rapidity in performance are described below.

Heterophile antibodies are those produced by the injection of one type of antigen and which are capable of reacting not only with the inciting antigen but also with unrelated antigens in related and unrelated species as well. The types of antibodies produced are agglutinins, lysins, opsonins, cytotropins, precipitins, anaphylactins and local or systemic toxins. Heterophile antigens (that is, those capable of producing heterophile antibodies) have been found in abundance throughout nature. They have been found chiefly in the lowest orders of animals, less frequently in the higher orders, especially the primates. They have also been found in species of birds, fish, reptiles, worms and in many bacteria but not in the higher plants. Though work along these lines started as early as 1899, it was the work of Forssman in 1911, that clarified the subject considerably and gave stimulus to further investigation. These studies were especially enhanced by Davidsohn[4,5] and more recently by Buchbinder[2].

Since heterophile antigens (Forssman type) are present in horses, it is to be expected that heterophile antibodies would be

produced in man after injection of therapeutic horse serums. In normal human serum these antibodies are found up to a dilution of 1:8, 1:16, and 1:32. An increase in titer of agglutinins and hemolysins up to 1:64 and 1:128 was demonstrated in serum sickness by Davidsohn and by Paul and Bunnell.

It was while they were investigating the blood of cases of rheumatic fever for heterophile antibodies (namely agglutinins and lysins) that Paul and Bunnell accidentally discovered them in high titer in a case of infectious mononucleosis in their control series. They confirmed this finding by demonstrating persistently high titers of these antibodies ranging from a dilution of 1:64 to 1:1024, in three other cases of infectious mononucleosis and reported their results in 1932. The titer of agglutinins in infectious mononucleosis rises usually after a latent period of 6 days following the onset of symptoms, reaches a peak and then decreases, disappearing gradually in some cases soon after, and in some, months after, recovery. According to Bernstein[1] there is no relation between the severity of the disease and the concentration of antibodies. There have been numerous other reports in the literature of cases of infectious mononucleosis with positive heterophile agglutination tests, confirming the findings of Paul and Bunnell. The specificity of the test has been amply demonstrated in large control groups by the various authors, but especially by Paul and Bunnell with 275 control cases and by Bernstein with 300 control cases.

In the report by Paul and Bunnell there was one apparently false positive test in the 275 controls, a case of aplastic anemia that had many transfusions, and presented agglutinins to a titer of 1:128. In Bernstein's series of 300 controls, there was one case of purpura hemorrhagica that had a titer of 1:128. There were unusual clinical features about these two cases that makes these results only questionably false positive reactions. In addition, Bernstein reported questionably false negative tests in two cases of possible infectious mononucleosis in children. The clinical findings here too were not entirely typical and in addition both children had pneumonia. Agglutinins were present in these cases to a titer of 1:4 and 1:16.

The technic of procedure used by these authors, was the same as that employed by Davidsohn in demonstrating heterophile agglutinins in serum sickness but as applied to infectious mononucleosis the procedure is commonly known as the Paul-Bunnell test.

TECHNIC

(1) Heat blood serum in water bath 15–30 minutes at 55°C.
(2) Make varying dilutions from 1:2 to 1:64 or more.
(3) To 0.5 cc. of diluted serum add 0.5 cc. of 2 per cent washed sheep cell suspension in saline.
(4) Add 1 cc. of saline to make volume up to 2 cc.
(5) Place in water bath 1 hour at 38°C.
(6) Leave in icebox overnight.
(7) Invert tube three times and read results.

Results are read according to the degree of clumping and recorded as 4+, 3+, 2+, 1+ and negative.

In an article by Butt and Foord[3], presenting a group of eighteen cases of infectious mononucleosis confirmed by the Paul-Bunnell test, mention is made of a hanging drop test that also appeared to confirm the diagnosis. The test consists of placing a loopful of sheep cells on a coverslip and then inverting it over a hollow ground slide. They claim immediate agglutination in cases of infectious mononucleosis and none in control cases.

Davidsohn[7] described a modified procedure to demonstrate the increased agglutinins in infectious mononucleosis that was considerably more rapid than the previous method.

TECHNIC

(1) Heat serum in water bath for 15–30 minutes at 55°C.
(2) Dilute serum 1:25 to 1:5,120.
(3) Place 0.25 cc. serum in 75 x 12 mm. test tubes.
(4) Add 0.1 cc. 2 per cent suspension of sheep cells in saline.
(5) Place in water bath at 38°C. for 1 hour.
(6) Place in icebox for 1 hour.
(7) Shake tubes and read. Results can be read through test tubes with the low power of the microscope.

This test, he claims, is definitely more sensitive than the previous method. In cases of infectious mononucleosis, titers up

to 1:5,120 were secured, and in serum sickness the titer was found as high as 1:320. In normal controls the titer may be as high as 1:40.

Towards the end of last year, an attempt was made to simplify and still further shorten the time for the performance of the heterophile antibody test utilizing the paraffin ring of Green[9] on 3 x 2″ glass slides similar to those used in the microscopic slide precipitation test for syphilis[10]. The following technic has been found satisfactory:

TECHNIC

(1) Heat sera in water bath at 56°C. for a half hour.
(2) Make dilutions 1:2 to 1:1024 or more.*
(3) Place 3 drops of the diluted serum from a Wright capillary pipette within the paraffin rings, on the glass slide.
(4) Add 1 drop of 2 per cent suspension of washed sheep cells.†
(5) Rotate 10 minutes and read under microscope.

Results are recorded according to the degree of clumping as in the tube tests. The varying degrees of clumping are more readily observed through the microscope by the slide test and weak reactions more clearly defined.

Mindful of the increased rapidity of agglutination of erythrocytes in blood typings by centrifugation as described by Wiener, a centrifuged tube test method for heterophile antibodies was also attempted and the following technic has been found satisfactory:

TECHNIC

(1) Heat sera for a half hour in water bath at 56°C.
(2) Make dilutions from 1:2 to 1:1024 or more.
(3) Place 1 cc. of diluted serum in test tubes.
(4) Add 1 cc. of 2 per cent suspension of washed sheep cells.
(5) Centrifuge for 5 minutes at about 2000 revolutions per minute.
(6) Shake and read.

The tubes are shaken by starting with the control tube, noting the vigor necessary to shake up the cells, then going to the tube with the highest dilutions and working down. Those with the lower dilutions show a single large red

* The dilutions referred to in the final reading are the initial dilutions of serums only, and are not concerned with the further dilution by cells.

† To secure the most sensitive results wash the sheep cells in saline and allow them to age in the icebox for several days[6, 12]

clump which is designated as 4+ agglutination. Smaller clumps are accordingly designated as 3+, 2+, and 1+. This tube method, on the whole, appears to be slightly more sensitive than the slide method. It was noted both in the slide and the tube methods, that if the serum was not heated, lysis of the sheep cells occurred in about the same degree as agglutination in the heated serum. This occurred without the addition of guinea pig complement as required by the methods employed by Davidsohn and by Paul and Bunnell. The probable explanation is that the concentration of complement normally present in human serum is sufficient for the reaction. This procedure is not satisfactory for testing highly colored serums or serums with hemolyzed erythrocytes.

After preparing the serum and making the serial dilutions the actual performance of the tests requires less than 10 minutes, therefore having a decided advantage over the Paul-Bunnell test which requires 13 hours, and over the Davidsohn modification, which requires 2 hours.

RESULTS

In the control series (table 1 contains a partial list) there were thirty-five cases of various conditions, acute and chronic, encountered in the routine procedure in the hospital. Strong agglutination was observed chiefly in the lower dilutions of 1:2 and 1:4 occasionally in dilutions of 1:8. In the majority of the control cases, agglutination was not observed in dilutions higher than 1:16, except for an occasional one plus or plus minus reaction in a dilution of 1:32.

There were two cases of type I lobar pneumonia (table 2) that had received antipneumococcus serum. The first, a child (case 19) 7 years of age, received 100,000 units, developed no serum sickness, and no increase of antibodies was apparently demonstrated. However, it should be noted that the degree of reaction in the lower dilutions up to 1:32 is slightly higher than seen in the controls, and suggests a slight increase of agglutinins. The change is too small to be definitely relied on. The second case, an adult female (case 20) 49 years of age received 120,000 units of the serum and did develop a mild serum reaction several days later. A definite increase of agglutinins up to a dilution of 1:256 was demonstrated by the tube method but no remarkable increase noted by the slide method.

In table 3 are five cases definitely diagnosed clinically as infectious mononucleosis. The first two were internes who had

TABLE 1

CONTROL CASES

DATE	NO.	SEX	AGE	METHOD	CONTROL	DILUTIONS									DIAGNOSIS
						2	4	8	16	32	64	128	256	512	1024	
7/23/35	1	F	39	S	−	++++	+++	±	−	−	−	−	−	−	−	Hypertensive cardiac
7/23/35	2	M	47	S	−	++++	−	−	−	−	−	−	−	−	−	Lues
7/23/35	3	F	46	S	−	++++	++	−	−	−	−	−	−	−	−	Rheumatic heart
7/23/35	4	M	25	S	−	+	−	−	−	−	−	−	−	−	−	Normal control
7/23/35	5	F	23	S	−	+++	++	±	−	−	−	−	−	−	−	Lues, acute sinusitis
7/23/35	6	M	26	S	−	+++	−	−	−	−	−	−	−	−	−	Hernia
7/23/35	7	F	39	S	−	++++	++	−	−	−	−	−	−	−	−	Hypertensive cardiac
7/25/35	8	M		S	−	++++	+++	+++	+	−	−	−	−	−	−	Lues
7/25/35	9	F	33	S	−	++++	++++	+++	++	±	−	−	−	−	−	Lues
7/25/35	10	F	55	S	−	++++	++++	++++	++	±	−	−	−	−	−	Infectious arthritis
7/25/35	11	F	52	S	−	+	+	−	−	−	−	−	−	−	−	Varicose ulcers
7/25/35	12	F	47	S	−	+++	+++	++	+	−	−	−	−	−	−	Menopause
7/25/35	13	M	8	S	−	+++	+++	+++	++	±	−	−	−	−	−	Congenital lues
10/ 1/35	14	M	35	S	−	+++	+++	+++	++	−	−	−	−	−	−	Cholelithiasis
10/ 8/35	15	F		S	−	+++	++	±	−	−	−	−	−	−	−	Pregnancy
10/ 8/35	16	M		S	−	+++	+++	++	+	−	−	−	−	−	−	Normal control
10/16/35	17	F	40	S	−	+++	+++	+++	++	+	±	−	−	−	−	Agranulocytic angina
10/16/35	18	M	61	S	−	+++	+++	++	++	+	−	−	−	−	−	Hemopneumothorax

S = slide test.

TABLE 2

Cases of Serum Sickness

DATE	NO.	SEX	AGE	BLOOD GROUP	METHOD	CONTROL	DILUTIONS 2	4	8	16	32	64	128	256	512	1024	REMARKS
12/ 7/35	19	M	7	IV	S	−	+++	+++	+++	+++	++	−	−	−	−	−	Lobar pneumonia. Type I serum but no reaction
12/ 7/35					T	−	++++	++++	++++	++	−	−	−	−	−	−	
1/22/36	20	F	49		S	−	++++	++++	++++	++	+	−	−	−	−	−	Lobar pneumonia. Type I serum with mild reaction
1/22/36					T	−	+++	++++	++++	++++	++++	++	++	+	−	−	

S = slide test. T = test tube test.

TABLE 3

Cases of Infectious Mononucleosis

DATE	NO.	SEX	AGE	BLOOD GROUP	METHOD	CONTROL	DILUTIONS 2	4	8	16	32	64	128	256	512	1024	REMARKS
7/26/35	21	M	26		S	−	++++	++	+	−	−	−	−	−	−	−	3 years old
7/29/35	22	M	27		S	−	+++	+++	+++	++	±	−	−	−	−	−	1 year old
10/ 1/35	23	F	21	IV	S	−	++++	++++	++++	++++	++++	++++	++++	−	−	−	Student nurse, typical clinical findings including blood picture
10/ 8/35					S	−	++++	++++	++++	+++	+++	++	++	+	±	−	
10/27/35					S	−	++++	++++	++++	++++	++++	+++	++	−	−	−	
10/27/35					T	−	++++	++++	++++	++++	++++	++++	+++	±	−	−	
12/12/35	24	M	28	II	S	−	++++	++++	++++	++++	+++	+++	+++	−	−	−	Interne, typical clinical findings including blood picture
12/12/35					T	−	++++	++++	++++	++++	++++	++++	++++	++++	+++	++	
12/12/35					P	−	++++	++++	++++	+++	+++	+++	++	++	−	−	
12/13/35					S	−	++++	++++	++++	++++	++++	++++	+	−	−	−	
12/14/35					T	−	++++	++++	++++	++++	++++	++++	++++	+++	+	+	
12/14/35					P	−	++++	++++	++++	+++	+++	+++	++	++	+	−	
12/30/35					T	−	++++	++++	+++	++	±	−	−	−	−	−	After recovery
6/ 5/36	25	M	19	IV	T	−	++++	++++	++++	++++	++++	++++	++++	++++	++++	+++	Typical case

S = slide test. T = test tube test. P = Paul-Bunell test.

TABLE 4

BORDERLINE CASES

DATE	NO.	SEX	AGE	BLOOD GROUP	METHOD	CONTROL	DILUTIONS										REMARKS
							2	4	8	16	32	64	128	256	512	1024	
11/25/35	26	M	4	IV	S	−	++++	++++	+++	++	±	−	−	−	−	−	Marked enlargement of spleen and liver. No pathological lymphocytes in smear
11/25/35					T	−	++++	++++	+++	++	+	−	−	−	−	−	
12/12/35					S	−	++++	++++	+++	+++	+++	++	−	−	−	−	
12/12/35					T	−	++++	++++	++++	++++	++++	−	−	−	−	−	
12/14/35					S	−	++++	+++	+++	++	±	−	−	−	−	−	
12/14/35					T	−	++++	++++	++++	++++	+++	++	−	−	−	−	
12/14/35					P	−	++++	+++	+++	++	+	±	−	−	−	−	
12/27/35	27	M	27	IV	S	−	+++	+++	+++	++	+	±	−	−	−	−	Considerable coal tar products for headache. Leukopenia with decrease in granulocytes
12/27/35					T	−	++++	++++	++++	++++	+++	++	−	−	−	−	
12/30/35					S	−	++++	++++	++++	+++	−	−	−	−	−	−	
12/30/35					T	−	++++	++++	+++	++	+	−	−	−	−	−	
12/14/35	28	F	19		S	−	++++	++++	+++	+++	±	−	−	−	−	−	Sore throat. Enlarged nodes. No fever
12/14/35					T	−	++++	++++	++++	++++	++++	−	−	−	−	−	
12/14/35					P	−	++++	++++	++++	++	++	±	−	−	−	−	

S = slide test. T = test tube test. P = Paul-Bunell test.

the disease, one 3 years previously and the other 1 year previously. Both at this time presented no increase of antibodies in the blood stream. The other three cases, one an interne, were in the active stage of the disease and were seen within a short time after the onset of their illness. The blood picture including the atypical lymphocytes and lymphocytosis and the clinical findings, were typical. They all presented agglutinins to a titer of 1:128 to 1:1024. The Paul-Bunnell tests performed in two of the cases at the same time appeared slightly less sensitive and showed agglutinins to be present to a titer of 1:256 to 1:512.

Table 4 presents three cases that were clinically diagnosed as infectious mononucleosis but each case presented several atypical features. The first, a male child (case 26) 4 years of age had a long course with fever, malaise, sore throat, generalized lymphadenopathy, leukocytosis with a relative and absolute lymphocytosis. No atypical lymphocytes were noted in the blood film. He presented an unusually large liver and spleen which extended almost to the iliac crest. Though at no time was the titer of agglutinins in the slide and tube methods and in the Paul-Bunnell test above 1:32 to 1:64, yet even this suggests a slight increase of antibodies since the degree of clumping in 1:32 was four plus. This case was attended by the interne (case 24) listed in the previous chart, and was also attended by the interne (case 27) discussed as the following case, an incident which offers further evidence for the infectious nature of the disease.

The second case is that of another interne (case 27), 27 years of age, who also attended the previous case on the pediatric service replacing the former interne when he became ill. He was admitted to the hospital on December 25, 1935 with the complaint of a headache, 6 to 7 days duration, a sore throat and malaise. Examination revealed ulcerated lesions in the pharynx, moderate cervical and axillary lymphadenopathy and a palpable spleen. His temperature remained at about 99.8°F. At first he developed a leukocytosis of 10,200 with 18 per cent polymorphonuclears, 77 per cent lymphocytes and 5 per cent monocytes. Atypical lymphocytes were noted in the blood film. He later developed a granulopenia with a leukocyte count of 5,800;

polymorphonuclears, 37 per cent; lymphocytes, 53 per cent; eosinophiles, 4 per cent; basophiles, 1 per cent; and monocytes, 5 per cent. He however, recovered gradually with symptomatic treatment and was discharged on January 12, 1936. The agglutination titer in this case ranged from 1:16 to 1:64 only, but the degree of clumping in these dilutions is considerably stronger than usual.

The third case a white female (case 28), 19 years of age developed the typical clinical and blood findings of infectious mononucleosis except that there was no fever, and showed but a slight increase in titer of agglutinins (1:32 to 1:64) by the slide, tube and Paul-Bunnell tests.

In these three cases the tests might be considered only weakly positive, the Paul-Bunnell tests being no more sensitive than the slide and tube tests. In such cases Davidsohn and Walker[3] have recently suggested a method for differential diagnosis. They have shown that these antibodies in infectious mononucleosis are not typically Forssman antibodies in that they are not completely absorbed out of solution by guinea pig tissues. Hence, if this procedure is applied to the serum in these border line cases and the antibodies are completely absorbed out, it can be concluded that they are not cases of infectious mononucleosis. If the antibodies are not absorbed out, they then can be considered as cases of infectious mononucleosis. I regret that the procedure was not attempted in these three questionable cases.

CONCLUSIONS

(1) Serological tests for heterophile antibodies offer invaluable aid in the diagnosis of infectious mononucleosis.

(2) While the number of cases thus far tested is small, the results suggest that the modifications presented here give results equal in specificity and sensitivity to the other tests and have the advantage of greater rapidity in performance.

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THE OCCURRENCE OF HETEROPHILE ANTIBODY (HEMAGGLUTININ) IN THE SERUM OF RABBITS SHOWING THE "SERUM SICKNESS" REACTION

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Since heterophile hemagglutinin is common to the majority of human cases of serum sickness, it occurred to us that the demonstration of agglutinins for sheep erythrocytes in the serum of rabbits showing the serum sickness reaction described by Fleisher and associates[2] might offer some additional proof for the basic identity of the reaction in man and in the rabbit. Davidsohn and Ramsdell[1] found no increase in agglutinin for sheep erythrocytes in a series of nine rabbits inoculated five times with 3 cc. of normal horse serum, the doses being given at 5 to 7 day intervals. Six of their animals did show, however, a pronounced development of lysin for sheep cells, the titers ranging from 1:128 to 1:512. The possibility, however, of heterophile agglutinin in rabbit serum sickness would not seem to be entirely ruled out by these observations in that the amount of serum necessary for the production of the reaction of serum sickness is much larger than they used and the behavior of the animal is quite different from that of an animal under immunization.

After determining that their normal heterophile hemagglutinin was not active above dilutions of 1:4, we inoculated ten white rabbits intravenously with a single dose of whole horse serum, each animal receiving 6 cc. of serum per kilogram of body weight, the total amounts ranging from 20 to 26 cc. in various animals.

Within the 10 days following all of the animals showed some degree of reaction, the erythema and edema of their ears varying from slight to moderate redness, the latter accompanied by a slight edema at the base and in the middle third of the ear. In

two animals the reaction was quite marked, in four others there was a moderate reaction, while the remaining animals showed only a slight reaction.

Tests for the presence of agglutinin for erythrocytes of sheep were started on the day following the serum injection and were repeated every other day for 30 days. Precipitin tests were included. In carrying out the agglutination tests equal quantities of serum dilutions and a 2 per cent suspension of erythrocytes of sheep were allowed to incubate for 2 hours at 37°C. following which the tests were allowed to stand at 10°C. over night. The same incubation was allowed for precipitin testing. The results were determined macroscopically.

In the two animals showing a marked serum sickness reaction, a slight increase in hemagglutinin titer began on the day after the height of the reaction (seventh) and gradually reached a maximum of a 1+ reaction at dilutions of 1:64 and 1:32, 3 weeks after inoculation. Agglutination was complete at 1:8 and 1:16. At the end of the fourth week the agglutinating titer had fallen gradually to 1+ at 1:16 and 2+ at 1:8. Agglutination was complete at 1:4.

Titers in the group showing a moderate reaction followed the same course but never became stronger than 1+ to 2+ reactions at a dilution of 1:32. Agglutinations at 1:16, however, were quite complete. The reactions remained the same for the three weeks following.

The remaining four animals showed only slight increases in hemagglutinating titer, these ranging around dilutions of 1:8 with an occasional 1+ reaction at 1:16.

Precipitin titers in all animals began a gradual increase 2 weeks after the inoculation and progressed uniformly to a maximum of 1:50 to 1:60 at the end of the fourth week.

While the agglutinating titer of the serum of these animals did not reach such levels as are commonly found in human serum sickness, the reactions were, on the whole, quite distinct. It would appear, then, that the occurrence of these antibodies offers some further information concerning serum sickness in rabbits. In addition to this, the behavior of these hemagglutinins to

absorption tests (reported in another paper) goes even a step farther in this direction and, we feel, offers certain additional possibilities to the study of some of the problems of heterophile antigens and antibodies.

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ON THE BEHAVIOR OF THE HETEROPHILE ANTIBODY (HEMAGGLUTININ) OF SERUM SICKNESS AND ACUTE INFECTIOUS MONONUCLEOSIS TO ABSORPTION WITH RAW AND AUTOCLAVED OX ERYTHROCYTES

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Bailey and Raffel[1] have recently shown that raw or autoclaved ox erythrocytes will absorb the hemolytic and hemagglutinative antibodies from the serum of patients with acute infectious mononucleosis. They also found that boiled or whole ox erythrocytes would not absorb the agglutinins for sheep cells in the serum of patients not having acute infectious mononucleosis but showing, never the less, high titers of agglutinin for sheep cells.

We have tested their findings in four cases of acute infectious mononucleosis, two cases showing a drug rash, and two cases of human serum sickness. In addition to these cases we applied their technic to the serum of rabbits which had developed hemagglutinins as a result of serum sickness reaction or as a result of prolonged treatment with large doses of whole horse serum.

In general our findings are quite in accord with theirs in that absorption in our cases of acute infectious mononucleosis removed almost entirely the sheep cell agglutinins but failed to remove the same antibodies in the other named conditions. (See table 1.)

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TABLE 1

RESULTS OF TESTS

CASE	AGGLUTINATION TITER	
	Before absorption	After absorption
Acute infectious mononucleosis		
1	1:128 (2+)	1.8 (±)
2	1:256 (1+)	1.8 (±)
3	1:64 (2+)	1.8 (1+)
4	1:128 (3+)	1.4 (1+)
Drug rash (Sodium morrhuate)		
1	1:64 (3+)	1:32 (2+)
2	1:32 (2+)	1:16 (2+)
Serum sickness (human)		
1	1:128 (2+)	1:32 (3+)
2	1:64 (3+)	1:32 (3+)
Serum sickness (rabbits)		
1	1:64 (1+)	1:16 (2+)
2	1:32 (2+)	1:16 (2+)
3, 4	1:32 (1+)	1:16 (2+)
5, 6	1:16 (2+)	1:8 (1+)
Immunized rabbits receiving 10 doses whole horse serum at 5 day intervals		
1, 2	1:64 (1+)	1:16 (2+)
3, 4, 5, 6, 7, 8	1:32 (2+)	1:16 (1+)
9, 10, 11	1:16 (2+)	1:16 (1+)

OSTEOBLASTIC SARCOMA OF THE UTERUS*

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The following case report of an osteoblastic sarcoma of the uterus is presented because of its apparent rarity and because of its contribution to the general problem of osteogenic sarcomas in unexpected areas as has been reported in kidney, breast and thyroid and soft tissues removed from and unattached to periosteum.

CASE REPORT

The patient, a housewife, 53 years old was admitted to St. Mary's Hospital, Walla Walla, Washington, June 30, 1935 with a history of pain and pressure in the lower abdomen and some frequency of urination for about a year. Her menopause was completed about six years ago. No discharge from the vagina was noted at that time. She had lost 20 pounds, but strength and endurance was unimpaired.

She had always been in excellent health; had had seven children, four living, one died at three, two were still born. She had an appendectomy at 45 years of age and a partial thyroidectomy for loss of weight and a heart "upset" at 44 years of age.

Physical examination revealed a well nourished, normal appearing female, with a temperature of 99 and pulse, 88, and respiration, 18. Blood pressure: 136/90. Examination was negative except for the lower abdomen. Here a marked tenderness and rigidity was elicited. A movable mass the size of a large walnut was present just below the umbilicus. Vaginal examination showed a normal cervix. The uterus was fixed and considerable pain was elicited upon attempting to manipulate it. The fundus was enlarged, broadened and very hard. No enlarged inguinal nodes were palpated.

A preoperative diagnosis of a malignant papillary cyst of the ovary with transplantation into omentum was made.

The patient was operated on July 15, 1935, the following being the findings: The uterus was found in normal position, quite large and rather fixed. It had a peculiar mottled red color as if there were areas or sinuses of blood. The organ was quite firm. Extending into the posterior cul-de-sac was apparently a por-

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tion of the uterus, a soft mass about 3 cm. in its longest diameter and approximately 4 mm. in thickness. This mass appeared to be a hemorrhagic cyst. The broad ligaments were uniformly indurated and of bony hardness, measuring approximately 2 cm. in thickness. All tissues were very friable and bled easily, making it difficult to remove the fundus intact. The cervix could therefore not be removed because of these operative difficulties. No enlarged lymph nodes were present in the pelvis but within the omentum, about 3 cm. from the transverse colon in the midline was a cystic mass about 4 cm. in its longest diameter. This was ruptured upon removal and was found filled with blood.

The immediate post operative course was uneventful. She returned to her home July 21, 1935. Soon after she began to notice increasing pain in her abdomen and distention requiring readmission to the hospital on August 15, 1935. Examination showed a recurrent mass filling the pelvis. This mass grew rapidly and extended upward causing much abdominal pain and distention. X-ray examination on September 14 showed a metastatic lesion within the lungs. The x-rays of the lower abdomen showed no apparent bony changes of the pelvis but these were unsatisfactory because of the density of the abdominal mass filling the pelvis and lower abdomen.

The patient died September 19, 1935. A postmortem examination unfortunately was denied.

Operative specimen

The specimen consisted of the fundus of the uterus, 1.5 × 8 × 7 cm. (fig. 1). The fallopian tubes and ovaries were attached in their normal positions and appeared grossly unaltered. Upon section the uterine canal was widely dilated by a broadly pedunculated hard mass that was very friable and readily broken from its base. This mass 6 × 4 × 3 cm. was cut with little resistance but a gritty sensation was transmitted to the knife. These areas were pin-point to pin-head in size and were irregularly scattered throughout the mass. The tissue otherwise appeared not unlike a fibromyoma in which areas of hemorrhage are present. The wall of the uterus at its widest point measured 2 cm. in thickness. It had a mottled reddish appearance. Such dark colored areas were cut with grit-like resistance and were scattered throughout the entire wall, more numerous in the region of the pedunculated mass and the left cornu. Numerous widely dilated blood sinuses were scattered throughout the wall. A second mass accompanied the uterus. This mass measured 5 × 4 cm. Externally it was roughened by fatty tissue. At one point a ruptured cyst like area could be made out. This mass was cut with little resistance and had an almost uniform grayish translucent appearance, except for some widely dilated blood sinuses and areas of hemorrhage.

Microscopic examination

Some sections (fig. 2) showed the myometrium and endometrium to be relatively unchanged. In the region of the tumor mass however, the myometrium

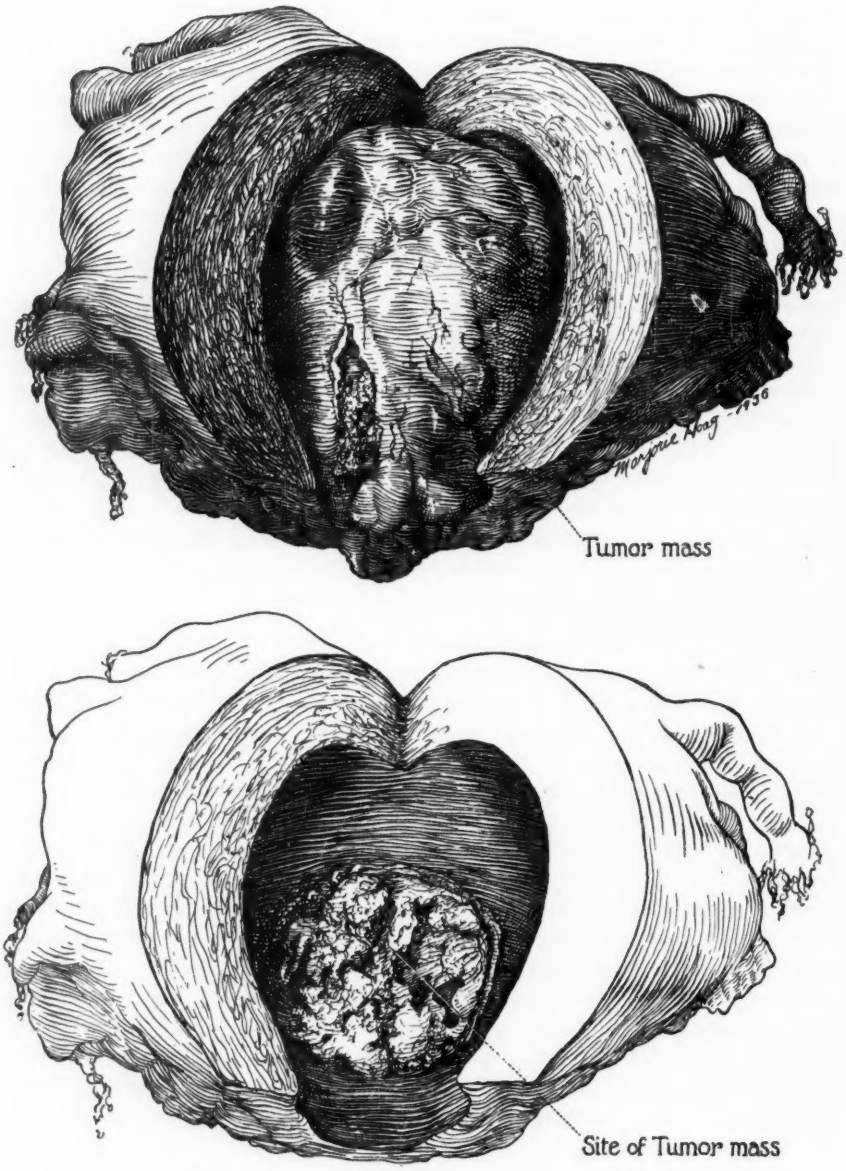

FIG. 1. UTERUS SHOWING TUMOR MASS BEFORE AND UTERUS AFTER REMOVAL OF THE MASS (¾ NATURAL SIZE)

was practically replaced by tumor tissue. The tumor mass within the uterus and the areas of tumor tissue within the uterine wall had a similar appearance. When occurring in compact masses the tumor cells were spindle shaped and had an oval vesicular staining nucleus among which were seen a moderate number that had mitotic figures and also an occasional evidence of giant cell formation. These giant cells had no more than ten to fifteen nuclei. Among such tumor

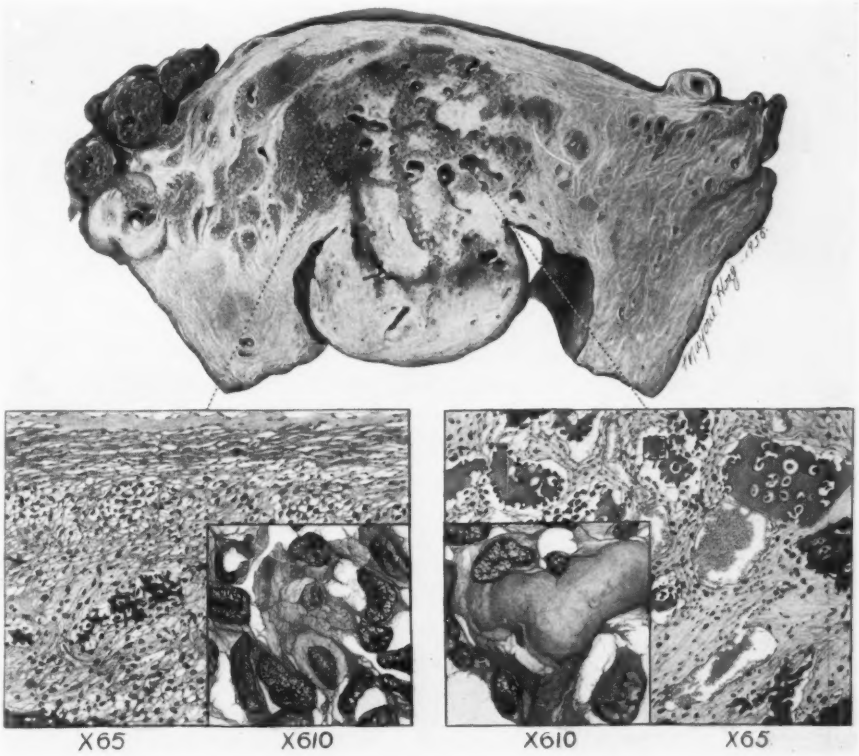

FIG. 2. CUT SURFACE OF TUMOR (¾ NATURAL SIZE) AND DRAWINGS FROM SECTIONS

cells an occasional strand of smooth muscle was evident. In the greater portion of the sections the tumor cells varied markedly in their size, shape and staining qualities. Many tumor giant cells were evident. Cells in active mitosis were the rule. The cytoplasm of the cells was frequently very abundant and vacuolated. Such tumor cells encircled and occurred within the broad zones of purplish staining bone-like masses, giving an appearance of all stages in transition from connective tissue to osteoid and partially matured bone.

Many widely dilated blood sinuses were present. These were frequently surrounded by the above described tumor cells and occasionally a mass of tumor tissue with deposits of bone-like tissue appeared to extend into the blood sinuses as a papillary-like mass. Sections of the mass outside of the uterus and attached to the omentum showed closely packed tumor cells extending into the surrounding fatty tissue. The tumor cells were more generally short spindle or oval shaped although in some areas comparatively long spindle cells were evident. The nuclei varied markedly in their size, shape and staining properties. These were frequently multilobulated and tumor giant cell formations were prominent features of the mass. Many mitotic figures were evident. The cytoplasm of the cells was frequently vacuolated. In contrast to the primary tumor within the uterus only an occasional deposit of a comparatively homogeneous purple staining material was found, irregularly scattered throughout these tumor cells. Only an occasional mass of oesteoid tissue could be identified. Many extensively dilated blood sinuses and diffuse areas of hemorrhage were evident. *Diagnosis:* Osteoblastic sarcoma of the uterus with extension to omentum.

DISCUSSION

The question which arises in this case is whether this is a true osteogenic sarcoma. There is definite indication in the primary tumor that there is a bone formation since we found all types of cells that must be interpreted to be osteoblastic since both osteoid and partially matured bone was evident.

There is no definite agreement as to the nature of the cell that forms bone. Kolodny[1] stated that the osteogenic sarcoma is a tumor derived from cells which are descendants of mesoblastic elements predestined embryologically to form bone. He gave as examples: typical bone formation in the lung and metastases of a far distant osteogenic sarcoma. On the other hand, Virchow[5] believed that all bone and cartilage, both normal and abnormal, arose by metaplasia from fibroblastic elements.

Mallory[3] who is more or less in accord with this view, called attention to bone formation in chronic inflammatory processes where the fibroblasts take on an osteoblastic function, similar processes taking place in a degenerating myofibroma of the uterus, the degenerating adenomas of the thyroid, et cetera. Leriche and Policard[2] went even farther and regarded osteosarcoma merely as a fibrosarcoma that has ossified. Mallory[4] supporting the theory that this is a metaplastic process presented a series of

bony and cartilaginous soft part tumors among which he cited a breast tumor in which osteogenesis occurred and where it was concluded that the tumor should be regarded as a fibrosarcoma with metaplastic foci of osteogenesis rather than a true osteoblastoma. The patient however developed no recurrence and therefore the tumor is not entirely comparable.

SUMMARY

This is a degenerating fibromyoma of the uterus which is undergoing a replacement by a neoplasm that is osteoblastic. The neoplasm has extended into the myometrium and apparently into the blood sinuses of the uterine wall. The process here has been comparatively slow and therefore comparatively well defined bone has been formed.

The process extended however into the omentum and from there the extension was rapid. The type of cells in this mass showed little osteogenesis and was more fibroblastic in character. Unfortunately no postmortem material is available to see the character of cells within the lungs. The x-ray did not give the impression of calcium deposits and only that of a tumor mass which one can theorize would be microscopically similar to that mass within the pelvis.

We are of the opinion that the tumor was an osteoblastic sarcoma of the uterus that probaby was of fibroblastic origin and by a metaplastic process produced osteoid tissue and true bone.

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THE ERROR OF DETERMINATION OF THE ERYTHROCYTE COUNT*

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> The element of error cannot be eliminated from our observations and our reasonings. The only true scientific method is to study it.—*J. F. Merz*

In a previous study[1] we made an examination of certain errors inherent in the enumeration of erythrocytes as made by the standard methods used in clinical laboratories. That study consisted in a statistical analysis of the variability of enumerations made in such a way that the personal error of the enumerator was eliminated. All the counts with which we were there concerned were effected by photographing the hemocytometer field and pricking through each cell on the photograph with a stylus connected to an electrical counter. For the details of the statistical methodology of analysis, the study referred to should be consulted. Since we are concerned in the present paper primarily with presenting some new experiments, we shall review only in brief outline our previous procedures and results.

We examined first the distribution of cells as they arrange themselves in the counting chamber. Theoretically, the counts in any subdivision of the chamber field should follow the Poisson series, and the variability measured as standard deviation should be given by $\sigma = \sqrt{m}$, where σ is the standard deviation† and

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† Throughout this paper, as in the previous one, the variability is discussed in terms of the *standard deviation* (S.D.), or in terms of the *coefficient of variation* (V.), which is the standard deviation expressed as a per cent of the mean value. Other expressions of variation are sometimes used, such as the average variation disregarding the sign, or the range of variation, which is the difference between the

m is the number of cells counted. But the conditions under which this would be true require that the cells be so diluted in the chamber that they do not affect each other's motion. This holds only approximately in the practical situation, for the cells do collide and otherwise influence the distribution. By making a number of complete enumerations of the field occupied by the entire chamber, using the photographic-mechanical method of counting, it was found that while the Poisson series gives a good approximation of the distribution, there is a systematic departure from the theoretical expectation in respect to the standard deviation, so that this is given by $0.92\sqrt{m}$ instead of $\sqrt{m}$. This variability we called the "variability of the field."

Examining certain other variations we considered as a unit: (1) the error of the count in the chamber as a whole; that is, the variation of the number of cells in one counting chamber as from another which would exist if samples from a single pipet were applied to different chambers. This variability includes what variation there might be among successive drops drawn from a single pipet as well as the variability arising from differences in the technic of placing a droplet in the chamber and also the differences in calibration of various chambers; (2) the error of the pipet as a whole; that is, the variability of the number of cells in one pipet from that in another, arising from variations of

largest and smallest observation. But, from statistical principles, the standard deviation is the most efficient and appropriate. This is because the standard deviation can be interpreted to give the percentage distribution of the original values. Within the limits of ±1 S.D. we can say that about two-thirds of the observations fall, and that outside of these limits the other third fall. Within limits of ±2 S.D. 95 per cent of the observations fall, and the other 5 per cent falls outside. Within ±3 S.D., 99.7 per cent fall, and the other 0.3 per cent falls outside, and so forth. It is the usual statistical practice to consider that an observation is significantly determined with ±2 S.D. This is because 95 per cent, or practically all of the observations fall within these limits. When, therefore, it is found that the S.D. of a count is 380,000 per cubic millimeters, for a count of 5,000,000 per cubic millimeters, or 7.7 per cent, expressed as coefficient of variation, it does not mean that these are the limits of variation but rather that the count is determined significantly within twice these values, that is, ±760,000 per cubic millimeter, or ±14.8 per cent.

dilution, calibration of pipets, and so forth, which would exist if an identical specimen were diluted separately in various pipets, and (3) the variability of the specimen as a whole; that is, the sampling variation of one specimen from another taken from the same individual, as for instance if numerous specimens were taken from separate punctures. We showed that the total error has the following relation to the errors enumerated:

$$\sigma_t = \sqrt{\frac{0.92^2 m}{n_f} + \frac{k_c^2 m^2}{n_c} + \frac{k_p^2 m^2}{n_p} + \frac{k_s^2 m^2}{n_s}}$$

where σt is the standard deviation of the total count $\times 10^{-4}$

m is the mean number of cells per eighty squares,

n_f is the number of blocks of eighty squares examined,

n_c is the number of chamber samples examined,

n_p is the number of pipet samples used,

k_c^2 is a constant measuring the variability associated with the procedure of placing a droplet in the counting chamber and evaluated as 0.00208, and

k_c^2 is a constant measuring the variability associated with the procedure of filling a pipet, evaluated as 0.00277.

The variability between specimens taken simultaneously from similar parts of the body was found to be zero within significant limits; in other words the value for k_s was zero and the last term under the square-root sign can therefore be disregarded.

From the formula given it was calculated that for a count of 5,000,000 erythrocytes, if a single field of eighty squares is examined, the standard deviation of the estimate would equal 405,000 cells per cubic millimeter; hence the count would be significantly determined within about $\pm$800,000 cells. It was pointed out that even if the whole 400 squares of the hemocytometer field were enumerated, the standard deviation of the estimate would be lessened by only a small amount as compared with its value when eighty squares were counted, and that the only way to make a material reduction in the error of estimate is to obtain an average of the counts made from different pipet samples on different chambers. Finally we showed that many of the present rules given in standard texts for agreement between successive

counts of blocks of squares, or successive counts from the same individual, are meaninglessly stringent, and that differences greater than those demanded by these rules are to be expected normally from 50 to more than 90 per cent of the time.

Desiring to investigate these problems further and to give, if possible, a value for the pipet constant (k_p) which would be based on a greater number of experiments, we repeated the determination of this value by adding to the series of twenty experiments

TABLE 1

SOME TYPICAL EXPERIMENTS TO EVALUATE THE VARIABILITY OF THE TOTAL ERYTHROCYTE COUNT

(Single specimen of blood, 10 pipets, 10 chambers in each experiment; enumeration made by the photographic-mechanical method)

COUNT NUMBER	EXPERIMENT NUMBER				
	1	2	3	4	5
1	630	402	495	423	478
2	523	360	464	366	376
3	586	381	461	465	340
4	505	410	513	422	393
5	520	363	500	375	413
6	541	336	450	456	439
7	526	421	482	438	405
8	548	469	572	417	405
9	544	378	444	445	364
10	531	437	523	355	405
Mean.....	545.4	395.7	490.4	416.2	391.8
S. D.....	36.8	40.0	39.1	40.5	28.1
V.....	6.7%	10.1%	8.0%	7.2%	7.2%

already published another like series of experiments with a different set of pipets. From a single puncture of each of twenty subjects, ten pipets were filled, and a sample from each of the pipets was placed in a separate counting chamber. Table 1 gives several typical protocols of these experiments. Counts of eighty squares were made on each chamber, and the results when combined with those previously published gave a value for $k_p^2 = 0.00217$ instead of the value 0.00277 as previously published. This gives a standard deviation of 38.56 or 386,000 cells per cubic

millimeter for a count of 5,000,000 erythrocytes per cubic millimeter, a value only 19,000 less than previously reported. The basic formula may be rewritten to express the variabilities in per cent, as the coefficient of variation $\left(\frac{\text{S.D.}}{\text{mean}} \times 100\right)$. So rewritten it becomes:

$$V_t = 100\sqrt{\frac{.92^2}{n_f \times m} + \frac{k_c^2}{n_c} + \frac{k_p^2}{n_p}}$$

where V_t is the variation of the estimate of the total count in per cent,

m is the mean number of cells per eighty squares,

n_f is the number of blocks of eighty squares examined,

n_c is the number of chamber samples examined,

n_p is the number of pipet samples used,

$k_c \times 100$ is the variation in per cent associated with the procedure of placing a droplet in the counting chamber evaluated as 4.5 per cent,

$k_p \times 100$ is the variation in per cent associated with the procedure of filling a pipet, evaluated as 4.7 per cent.

The percentage variation due to the field is dependent on the mean count and for 5,000,000 cells is 4.1 per cent. The percentage variation of the chamber and pipet are independent of the mean count.

If the count is made by taking a single pipet specimen and enumerating the cells in eighty squares, the variation will be as follows: For a count of 5,000,000, ($m = 500$) $V_t = 7.7$ per cent; for a count of 6,000,000, ($m = 600$) $V_t = 7.5$ per cent; for a count of 4,000,000, ($m = 400$) $V_t = 7.9$ per cent; for a count of 3,000,000, ($m = 300$) $V_t = 8.4$ per cent.

In order to investigate the effect of the calibration error on the total error of the chamber and of the pipet, we obtained through the courtesy of officials of the Bureau of Standards of Washington, ten calibrated chambers and twenty-six calibrated pipets. We then made a series of ten counts from each of twenty pools of blood (200 counts in all), using the calibrated chambers and pipets. Counts of eighty squares from each

chamber were made (table 2). By making calculations of the variability of the counts without the calibration corrections, and then with the calibration corrections applied, we determined the error ascribable to calibration as contrasted with all the rest of

TABLE 2

TYPICAL EXPERIMENT TO DETERMINE THE EFFECT OF THE CALIBRATION ERROR OF CHAMBER AND PIPET

(Single specimen of blood, ten pipets, ten chambers, eighty squares; enumerated by photographic-mechanical method)

COUNT NUMBER	UNCORRECTED	CALIBRATION CORRECTION APPLIED		
		Chamber	Pipet	Chamber and pipet
1	461	470	465	474
2	487	502	486	501
3	438	448	435	446
4	502	514	496	508
5	498	504	494	500
6	449	450	452	453
7	497	494	497	494
8	507	503	510	506
9	480	483	481	484
10	517	517	518	518
Mean.....	483.6	488.5	483.9	483.6
S. D.....	26.2	25.0	25.9	24.0

the variability due to the use of each instrument. In this way we determined that:

$$k_{c1} \times 100 = 2.9 \text{ per cent}$$
$$k_{c2} \times 100 = 3.5 \text{ per cent}$$
$$k_{p1} \times 100 = 1.7 \text{ per cent}$$
$$k_{p2} \times 100 = 4.3 \text{ per cent}$$

where $k_{c1} \times 100$ is the chamber error due to calibration, in per cent,

$k_{c2} \times 100$ is the rest of the chamber error, in per cent,

$k_{p1} \times 100$ is the pipet error due to calibration, in per cent,

$k_{p2} \times 100$ is the rest of the pipet error, in per cent.

We may now write for the total error of estimate in per cent when a single specimen is counted:

$$V_t = 100\sqrt{\frac{.92^2}{m} + k_{c1}^2 + k_{c2}^2 + k_{p1}^2 + k_{p2}^2}$$

It is enlightening to inquire into the effect of changing particular constituents of the total error. If perfect chambers and pipets are used, k_{c1} and k_{p1} become zero. The total error then (for a mean count of 5,000,000) is reduced from 7.7 per cent to 7.1 per cent. In terms of total count this would mean a difference

TABLE 3

ENUMERATION OF 80 SQUARES BY ESPECIALLY TRAINED TECHNICIANS

EXPERIMENT NUMBER	METHOD		DIFFERENCE
	Eye	Mechanical	
1	501	488	+13
2	296	292	+4
3	676	683	−7
4	469	470	−1
5	463	446	+17
6	396	401	−5
7	519	534	−15
8	642	659	−17
9	520	516	+4
10	502	495	+7
	Mean mechanical count = 498.4		
	Mean difference = 0.0		
	S. D. differences = 10.6		
	V. differences = 2.1%		

in the standard deviations of 30,000 cells. If both the calibration errors were doubled, the total error would be raised to 9.6 per cent.

In the discussion up to this point, we considered errors arising from procedures and instruments. The personal error of counting involved in making an enumeration by examining visually the hemocytometer field was omitted, since all the enumerations which we considered were made by the mechanical method. We next undertook to evaluate the personal error involved in making the count by eye. This was done by arranging to have a series

TABLE 4

ENUMERATION OF 80 SQUARES BY GRADUATES IN MEDICINE

EXPERIMENT NUMBER	METHOD		DIFFERENCE	EXPERIMENT NUMBER	METHOD		DIFFERENCE
	Eye	Mechanical			Eye	Mechanical	
1	576	591	−15	16	454	453	+1
2	534	563	−29	17	488	487	+1
3	527	540	−13	18	487	511	−24
4	521	540	−19	19	410	461	−51
5	487	495	−8	20	497	512	−33
6	528	539	−11	21	535	536	−1
7	476	500	−24	22	468	470	−2
8	438	487	−49	23	479	505	−26
9	561	551	+10	24	474	496	−22
10	497	490	+7	25	558	570	−12
11	498	493	+5	26	477	504	−27
12	430	444	−14	27	337	325	+12
13	518	512	+6	28	339	341	−2
14	532	536	−4	29	360	348	+12
15	466	460	+6	30	403	401	+2

Mean mechanical count = 483.5
Mean difference = −10.8
S. D. differences = 16.7
V. differences = 3.4%

TABLE 5

ENUMERATION OF 80 SQUARES BY ROUTINE TECHNICIANS

EXPERIMENT NUMBER	METHOD		DIFFERENCE	EXPERIMENT NUMBER	METHOD		DIFFERENCE
	Eye	Mechanical			Eye	Mechanical	
1	464	544	−80	11	453	526	−73
2	409	469	−60	12	444	503	−59
3	395	460	−65	13	469	540	−71
4	450	505	−55	14	428	479	−51
5	425	499	−74	15	458	464	−6
6	480	509	−29	16	440	481	−41
7	434	479	−45	17	434	478	−44
8	436	475	−39	18	435	498	−63
9	446	481	−25	19	432	485	−53
10	481	564	−83	20	411	471	−60

Mean mechanical count = 495.5
Mean difference = −53.8
S. D. differences = 19.0
V. differences = 3.8%

of counts (eighty squares in blocks of twenty squares across the chamber at a magnification of 100 diameters) made in the usual manner by eye, and then photographing and enumerating the identical field examined with the mechanical counter. Three classes of individuals were used in these experiments: (1) a group of technicians who were especially trained for assistance in hematologic research, (2) a group of technicians who had the usual training for, and were occupied in, routine hospital laboratory blood work, and (3) a group of graduates in medicine who agreed to coöperate and make an enumeration as they would for a patient being examined. In tables 3, 4, and 5 are shown the results for these three groups.

For the group of specially trained technicians (two individuals, ten enumerations) it was found that the discrepancies of eye counts from the correct counts made mechanically varied equally above and below the true counts, so that the average discrepancy was zero. However, the variation of these discrepancies around the zero value was considerable. The standard deviation of these discrepancies was determined as 10.6 for a mean count of 498, or a coefficient of variation of 2.1 per cent. The effect of this error on the variability of the total count is to add itself to the previously enumerated errors in the manner illustrated for the other constituent errors which have been discussed. To evaluate the total error, therefore, we add to the square of the previously determined error the square of the present one, the square root of the sum giving the total variation. Thus for a count of 5,000,000 cells per cubic millimeter, the errors previously discussed correspond to 7.7 per cent; together with an observation error of 2.1 per cent, it gives a total error of 8.0 per cent.

The group of ordinarily trained technicians (five individuals, twenty experiments) did not show a random distribution, plus and minus, of the discrepancies of eye count and true count. On the contrary, all were negative; that is, the eye counts were all less than the true counts. The average discrepancy for this group was minus 53.8 for a mean correct count of 495.5, or minus 10.9 per cent. The standard deviation of the discrepancies was 19.0, giving a coefficient of variation of 3.8 per cent. The

type of error encountered here is different from any so far considered in that it is *systematic*; that is, it has a predominant tendency in one direction, namely, negative. If we knew this definitely for a particular group of counts, it would be proper to increase systematically each enumeration by about 10.9 per cent. Assuming this correction to be made, the total variation is calculated as before by adding the square of the variation 3.8 per cent to the square of previous error and obtaining the square root of the sum. This gives for a count of 5,000,000 per cubic millimeter a total variation of 8.6 per cent. If the systematic correction were not effected but the counts made by eye used directly, we should have to add also the square of the average discrepancy 10.9 per cent. This yields a total variability of 13.9 per cent for counts made under these conditions.

The group of graduates in medicine (ten individuals, thirty experiments) gave a result intermediate between those for the other two groups. The average discrepancy was in the negative direction and amounted to minus 10.8 in a mean count of 484 or minus 2.2 per cent; the standard deviation was 16.7, yielding therefore a coefficient of variation of 3.4 per cent. As in the case of the ordinarily trained technicians one could properly increase the counts obtained by eye from such a group of individuals systematically, in this case by 2.2 per cent. The total error would then be obtained by adding the variability, 3.4 per cent, as before; the value of the total variation then comes to 8.4 per cent. Without the systematic correction the variability comes to 8.7 per cent.

It is not suggested that systematic corrections, of the character and amounts used, can be practically applied to enumerations as ordinarily made. It was seen that the discrepancies of eye counts from correct counts vary according to the training of the persons who do the counting. Hence no general correction can be applied. The calculations were given to show how various deviations affect the total error of enumeration. In any case it is seen that the variability of an enumeration made from a single specimen measured as coefficient of variation is at least about 8 per cent, and in the case of routine technicians will be about 14

per cent. This means that such a count can be relied on only from within ± 16 per cent to ± 28 per cent (twice the coefficient of variation) depending on the training of the individuals who made the eye count.

CONCLUSIONS

On the basis of further investigation and a longer series of observations, the standard deviation of the total count, estimated from an enumeration of cells in eighty squares of the hemocytometer chamber by the photographic-mechanical method described in the text for an individual whose erythrocyte count is about 5,000,000 cells per cubic millimeter, is about 385,000, giving a coefficient of variation of 7.7 per cent. In terms of the usual statistical limits of significance (twice the standard deviation) the estimate made by this procedure is therefore determined significantly within about ± 770,000 cells per cubic millimeter or ± 15 per cent.

The effect of errors of calibration of chambers and pipets* was found to be relatively small. Thus if pipets and chambers had no calibration error the total error (for a mean count of 5,000,000 cells) would be reduced from 7.7 per cent to 7.1 per cent expressed as a coefficient of variation, or by 30,000 cells when compared with an estimate obtained with the use of pipets and chambers as furnished by a reliable supply house.

Unless one is greatly experienced, carefully trained, and by nature accurate, there will result a large error due to inability to make an accurate count by eye. As a rule the count will be too low, and with routine technicians will be of the order of 10 per cent. With well-trained young physicians, the mean error may be expected to average about one-fifth as great. Technicians can be trained so that their average error is zero; but the individual enumerations are still variable from the true count and this variability raises the error of the estimate of the count made from an examination of eighty squares from 7.7 per cent, when made by the mechanical counting method, to 8.0 per cent, when

*Apparatus obtained from open stock of Arthur H. Thomas Co., Philadelphia.

made by eye under these conditions. The determination made from an eye count of eighty squares is therefore reliable only to within ± 16 per cent.

REFERENCE

(1) Berkson, Jos., Magath, Thomas B., and Hurn, Margaret: Laboratory standards in relation to chance fluctuations of the erythrocyte count as estimated with the hemocytometer. Jour. Am. Statis. Assn., **30:** 414–426. 1935.

HEMOLOGIC OBSERVATIONS ON SICKLE CELL ANEMIA

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Since Herrick[6] in 1910 described elongated and sickle-shaped erythrocytes in a case of severe anemia the sickle cell trait has been considered a perplexing hemologic problem. Most investigators of record agree that the sickling trait in the presence of anemia connotes a definite clinical entity.

Until Cooley and Lee[3] reported sickle cell anemia in a four year old (American-born) Greek boy it was generally believed that the sickling phenomenon was an ethnic characteristic of the negro. Since Cooley and Lee asserted that "the general acceptance of the dictum that sickle cell is peculiar to the negro race has beer too precipitate," several cases have been reported as occurring in Italians, Sicilians, and even in a boy of Scotch-Irish parentage.

The three patients constituting this report on hemologic observations of sickle-cell anemia were of Afro-American parentage beyond any reasonable doubt. Patient 1, 15 years of age, had a dark tan complexion, kinky hair, and bluish gums and nail beds, while patient 2, 25 years of age, had a "café au lait" coloring, with unmistakable negroid features. This patient is of interest since she was in the third trimester of pregnancy when a severe sickle cell anemia was found. Lash[8] reported that sickle cell anemia in pregnancy had been mentioned only twice in the literature previous to his description of a 21 year old colored primipara, who died apparently of an arterial thrombosis of the liver following cesarean section. The third patient (case 3, table 1), was a negro, 23 years of age, having all the characteristics of an Afro-American.

Washburn,[13] Cook and Meyer,[1] Emmel,[4] Sydenstricker, Mul-

TABLE 1

COMPARATIVE ERYTHROCYTE AND LEUKOCYTE PATTERN OF THREE CASES OF SICKLE CELL ANEMIA

CASE	SEX	AGE	ASSOCIATED ENTITY	DATE	ERYTHROCYTES	HEMOGLOBIN	PLATELETS	RETICULOCYTES	MEGALOBLASTS***	NORMOBLASTS	DIAMETER ERYTHROCYTES	LEUKOCYTES	MYELOCYTES	JUVENITS	STAB FORMS	SEGMENTED FORMS	EOSINOPHILS	BASOPHILS	LYMPHOCYTES	MONOCYTES
					millions	*per cent*	*thousands*	*per cent*			*microns*		*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1	♀	16 yrs.	Uterine bleeding	December '32	2.5	52	—	—	—	—	—	14,200				57	1		38	4
				December '32	2.3	52	—	—	—	—	—	14,000				48	1		49	2
				January '33	2.0	46	90	26.7		18	8.0	10,400		12	11	34	3	2	35	3
				February '33	2.1	51	—	24.2		3.9	—	11,250		7	15	32	6	3	32	5
2	♀	26 yrs.	Pregnancy	February '36	0.9	25	110	20.2	28	56**	8.1	11,400	1	2	26	48	2	1	18	2
				March '36	2.38	48	185	14.2	2	33	7.8	11,700		3	14	56	3	1	20	3
				April '36	3.6	65	276	10.0	—	13	7.6	15,050			14	50	7	2	25	2
3	♂	23 yrs.	None	January '36	2.1	46	210	24.5	—	4	7.8	8,150		2	8	14	2	2	70	2
				February '36	2.2	44	230	22.8	2	33	7.8	8,350		3	10	15	2	1	67	2
4*	♀	1 day	None	April '36	5.8	120	498	4.0	—	52	7.3	17,250	1	1	14	52	3	2	23	4
		1 wk.		April '36	5.0	130	486	3.1	—	—	7.4	8,350			6	26	1	1	63	3

* Blood count of baby of patient 2 born during this study.

** 12 per cent microblasts.

*** Number observed while enumerating 100 leukocytes.

herin and Houseal,[12] Huck,[7] Cooley and Lee,[2] Graham,[5] and Mason[9] are among those who made initial observations on various aspects of sickle cell anemia. Steinberg[10] published a valuable review on its clinical and laboratory features. Bone marrow studies on sickle cell anemia seem to have been described infrequently. Sydenstricker[11] found the bone marrow to be abundant, bright red in color and thin in consistency. Huck confirmed

TABLE 2

DIFFERENTIAL CELL COUNTS ON BONE MARROW OF TWO CASES OF SICKLE CELL ANEMIA

CELLULAR ELEMENTS	PATIENT 2 ♀	PATIENT 3 ♂
	per cent	*per cent*
Leukocytes		
Leukoblasts	3	3
Premyelocytes	7	10
Myelocytes, eosinophilic	3	4
Myelocytes, basophilic	1	1
Myelocytes, neutrophilic	13	18
Metamyelocytes, juvenil	17	23
Neutrophil, stab	20	18
Neutrophil, segmented	25	15
Eosinophils	5	2
Basophils	1	1
Lymphocytes	3	4
Monocytes	2	1
Erythrocytes		
Reticulocytes	15.8*	21.2*
Megaloblasts	12.0	3.2
Normoblasts	40.0	12.8
Mean diameter	7.8μ	7.8μ

* Reticulocytes given in per cent of erythrocytes and were counted separately after vital staining.

these observations. Our studies on bone marrow removed through sternal puncture conform to the foregoing qualities.

In addition various qualitative and quantitative studies on bone marrow and peripheral blood of an adult negro were compared with similar observations made on an adult negress (table 2). The peripheral blood patterns of these two cases during their anemic phase were also compared with that of another patient

with sickle cell anemia found in an adolescent negress (Patient 1, table 1), who was initially admitted to the Anemia Laboratory for study on account of prolonged functional uterine bleeding.

HEMOLOGIC OBSERVATIONS

The hemologic observations on patient 2 are recorded in table 3.

Among 100 leukocytes were found 28 per cent megaloblasts, 44 per cent normoblasts and 12 per cent microblasts. The reticulocytes were predominantly young types showing heavy

TABLE 3

PATIENT 2. PERIPHERAL BLOOD

(Negress, 26 years of age, third trimester of pregnancy)

Erythrocytes	940,000 per cu. mm.
Mean diameter	8.1 microns
Thrombocytes	110,000 per cu. mm.
Reticulocytes	20.2 per cent
Hemoglobin	25.0 per cent (Newcomer)
Bleeding time	4.5 minutes
Coagulation time	3.0 minutes
Fragility	0.38 to 0.28 per cent sodium chloride
Leukocytes	11,460 per cu. mm.
Myelocytes	1 per cent
Metamyelocytes, juvenils	2 per cent
Neutrophils, stab	26 per cent
Neutrophils, segmented	49 per cent
Eosinophiles	1 per cent
Basophiles	1 per cent
Lymphocytes	18 per cent
Monocytes	2 per cent

wreath-forms of reticulation. There was marked anisocytosis, poikilocytosis and polychromasia. Many stippled erythrocytes were found along with a small number of ovalocytes. The thrombocytes varied in size and appeared toxic.

An initial wet, sealed preparation of peripheral blood showed approximately 85 per cent sickle cells. While the photomicrographs were made on specimens taken at a later date, figure 6 depicts extensive sickling.

The neutrophilic series showed a severe left shift of a degenerative type. All the neutrophils manifested various degrees of

toxic changes, the segmented forms especially exhibited large clumps of coarse, basophilic cytoplasmic granules.

The lymphoid series were normal. The monocytes showed abnormal vacuolation.

While studies were being carried out on patient 2, she was given several whole blood transfusions. Whether the erythrocytes were made more susceptible to lysis thereby cannot be determined. Figure 8 shows the peripheral blood after standing 6 days at room temperature. Erythrocytic disintegration was well advanced beyond that observed in a preparation of peripheral blood from patient 3, table 1, held under identical conditions.

The differential cytologic studies on the bone marrow, cited in table 2, indicate a tendency toward erythropoietic and myelopoietic hyperplasia in patient 2. The quantitative data on the bone marrow of patient 3, however, conform to a normal pattern. A slight hyperneocytosis in the adult negress would be expected owing to the severity of the anemia. Pregnancy with or without anemia, also, usually is accompanied by some degree of myeloid immaturity. It is noteworthy that the differential pictures found in both bone marrow preparations are consistent with their respective peripheral blood patterns.

Eight photomicrographs depicting natural and induced changes in bone marrow and peripheral blood preparations of patient 2 are submitted. While the legends appended explain the procedure in each instance, attention is invited particularly to figures 2, 3 and 4. In these procedures the sickling phenomenon of the bone marrow cells was completely dissipated by washing in saline solution, returned when the patient's serum was added to the washed cells and persisted when the washed cells were added to normal blood serum collected from an adult male of the same blood type. On the other hand, blood cells from the normal adult male of the same blood type did not show any morphologic change when sealed in the serum of patient 2 for 6 days.

Patient 2 was delivered 47 days after the first blood study was made. A blood count was taken on the baby immediately after birth. No sickling was found to occur in a sealed wet

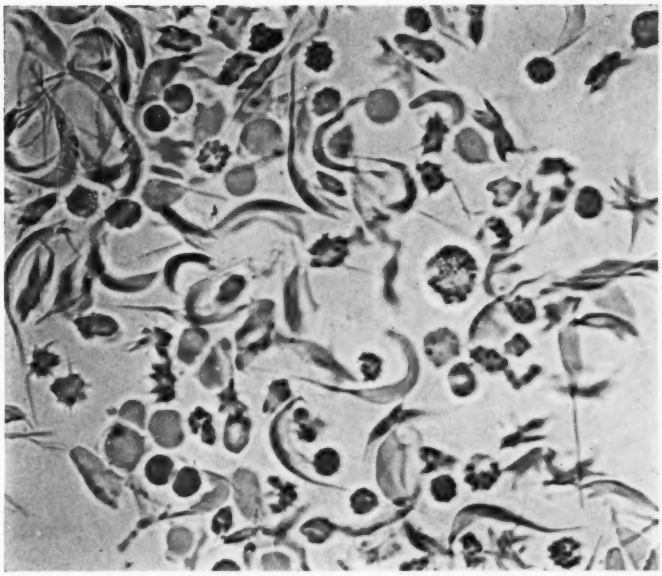

FIG. 1. PHOTOMICROGRAPH OF A WET, SEALED PREPARATION OF BONE MARROW TAKEN IMMEDIATELY AFTER REMOVAL FROM PATIENT 2

The sickling phenomenon is extreme, the cells manifesting polar threads which are readily demonstrated under high magnification. × 1500

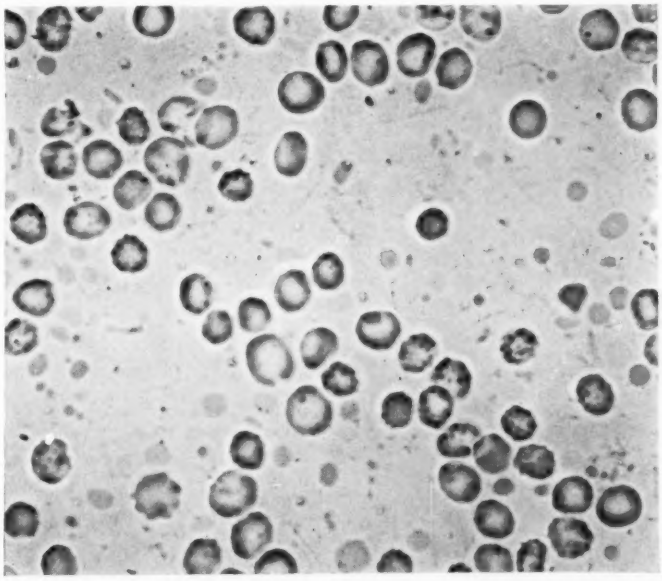

FIG. 2. PHOTOMICROGRAPH OF BONE MARROW TAKEN FROM PATIENT 2

The bone marrow was washed continuously in 0.85 per cent saline soluton until the erythrocytic elements regained a normal contour. While crenation and distortion are present, the majority of the cells show a fairly normal morphology. × 1500

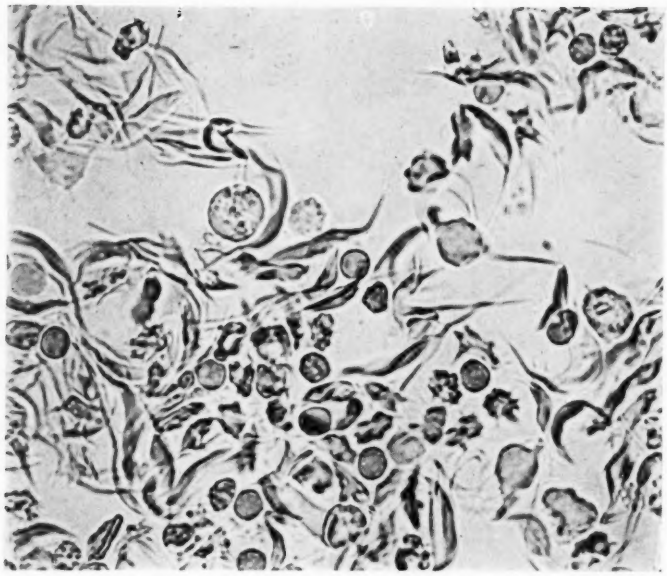

FIG. 3. PHOTOMICROGRAPHS OF THE WASHED BONE MARROW PREPARATION ILLUSTRATED IN FIGURE 2, AFTER BREAKING THE SEAL AND ADDING BLOOD SERUM FROM PATIENT 2

The sickling phenomenon recurred at the end of 6 hours. × 1500.

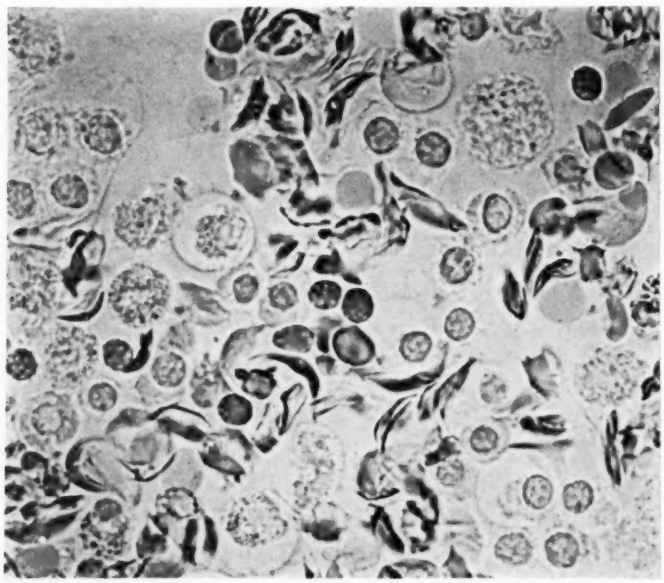

FIG. 4. PHOTOMICROGRAPH OF BONE MARROW FROM PATIENT 2, AFTER WASHING IN 0.85 PER CENT SALT SOLUTION AND BEING SEALED IN BLOOD SERUM FROM A NORMAL ADULT MALE OF THE SAME BLOOD TYPE (TYPE 4)

The photograph was made 6 hours after the serum was added to the washed bone marrow. × 1500.

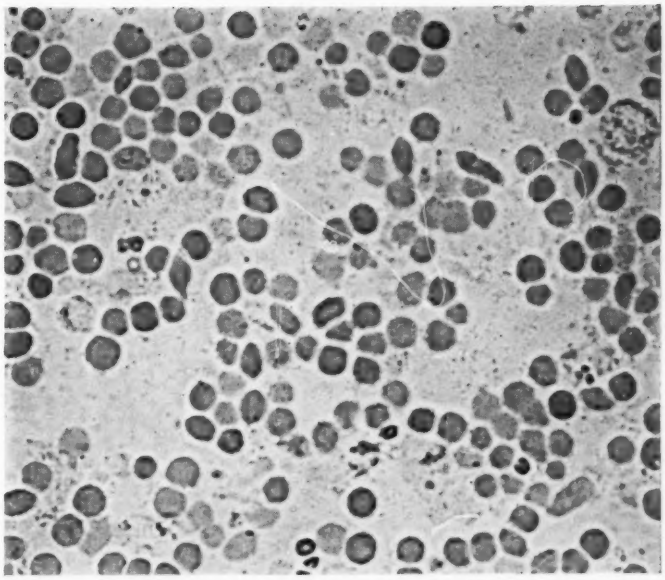

FIG. 5. PHOTOMICROGRAPH OF BONE MARROW FROM PATIENT 2, WASHED WITH 0.85 PER CENT SOLUTION, SEALED AND ALLOWED TO STAND AT ROOM TEMPERATURE FOR 7 DAYS

There is an appreciable loss of cellular pigment and advanced erythrocytolysis. × 1500.

FIG. 6. PHOTOMICROGRAPH OF A WET, SEALED PREPARATION OF PERIPHERAL BLOOD 6 HOURS AFTER BEING COLLECTED FROM PATIENT 2

The erythrocytic pattern at the time this photograph was made is described in table 1. The sickling phenomenon is equally as extreme as that demonstrated in the bone marrow preparation, figure 1. The cells show the same polar threading. × 1500.

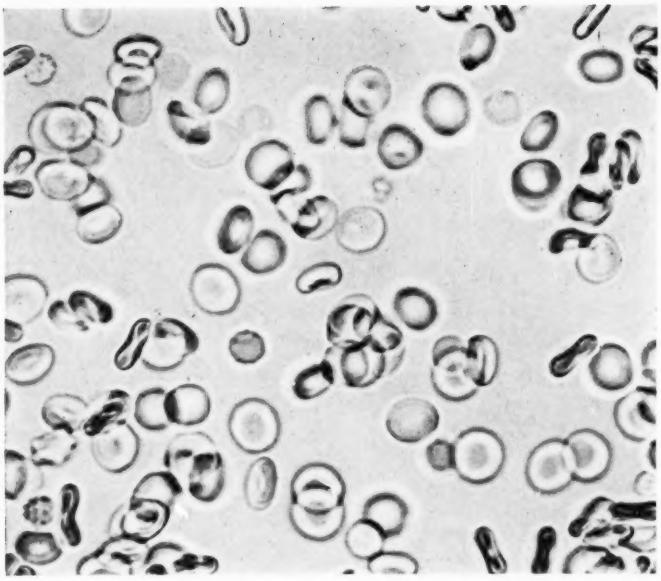

FIG. 7. PHOTOMICROGRAPH OF A WET, SEALED PREPARATION MADE OF BLOOD SERUM FROM PATIENT 2, TO WHICH WAS ADDED WHOLE BLOOD FROM A NORMAL ADULT MALE OF THE SAME BLOOD TYPE (TYPE 4)

The photograph was taken 6 days later. The morphology of the erythrocytes remained entirely normal. × 1500.

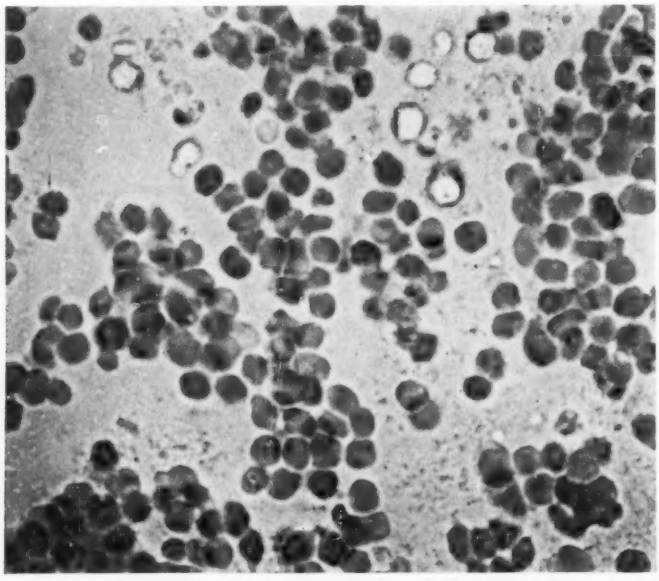

FIG. 8. PHOTOMICROGRAPH OF A WET PREPARATION OF PERIPHERAL BLOOD TAKEN FROM PATIENT 2 AND MAINTAINED UNDER SEALED CONDITIONS FOR 6 DAYS

The lytic process is comparable to that found in the bone marrow preparation, figure 5. × 1500.

preparation of peripheral blood during a week's observation, but the phenomenon did appear during the fourth month.

SUMMARY

(1) Three cases of sickle cell anemia are presented. One patient was confined during the hemologic study. The infant, a female, showed neither the sickling trait nor an anemia.

(2) Quantitative hemologic data on bone marrow and peripheral blood preparations are given on two of the three cases. Although both were severely anemic the peripheral blood of the negress only showed an appreciable immaturity. The bone marrow cell counts on both patients were slightly above normal but to a greater degree in the negress.

(3) Severe anemia or pregnancy will induce erythropoietic and myelopoietic immaturity.

(4) Natural and induced changes in peripheral blood and bone marrow preparations are submitted in a series of photomicrographs. These observations demonstrate that the sickling trait of the erythrocytes can be overcome by washing in saline and reinduced by addition of the patient's blood serum.

(5) Sickling occurs in bone marrow cells of sickle cell anemia when sealed in normal serum from an individual of the same blood type.

(6) Blood cells from a normal individual of the same blood type retain their normal contour when in contact with serum from a case of sickle cell anemia for a period of 6 days.

(7) The offspring of a patient showing a severe sickle cell anemia did not manifest the sickling trait immediately after birth.

The authors acknowledge with thanks the opportunity accorded to them by members of the staffs of Harper Hospital and Herman Kiefer Hospital, Detroit, to study patients 2, 3 and 4.

We gratefully acknowledge also the interest and able assistance of Mr. Frank N. Ruslander, of Harper Hospital, who made the photomicrographs.

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EDITORIAL

The Conference on the Serologic Diagnosis of Syphilis from the Viewpoint of the Serologist

It is now more than a year since there appeared "The Evaluation of Serodiagnostic Tests for Syphilis in the United States" which presented the results of the study of 954 specimens of blood serum and 220 specimens of spinal fluid by thirteen American serologists. Several interpretations of this report have appeared including the original comment of the Evaluation Committee and it is apparent that no unanimity of opinion can be expected on the subject. It is quite possible that one should no more expect unanimity on this subject than as to the best make of automobile among the several in one price range.

In this study the tests were carried out each by its author or a serologist closely associated with him. Under such circumstances it is to be expected that the execution of the tests would be practically perfect and the results in all probability superior to those obtained with the same tests carried out by the usual technicians in the average hospital or commercial laboratory. If this likelihood is accepted as valid then the choice of a test in any given laboratory might well depend upon such factors as familiarity with some special technic, special capabilities or incapacities of individual technicians, personal preferences of the laboratory director or local conditions controlling available space and time. Under these circumstances it would be quite possible for a laboratory using an "inferior" (so-called) test to obtain results that are quite as good or even better than those obtained in another laboratory using the "best" test.

One of the sources of difficulty in evaluating these tests is the fact that it has been found necessary to express relative sensitivity and specificity in terms of percentage and there is thus created an exaggerated idea of the differences between tests. So, for exam-

ple, three methods that score 82.4 per cent, 82.5 per cent and 84.6 per cent respectively cannot justly be said to show a detectable difference in rating. The figures are obtained with a total of about one thousand tests, a number that is too small to permit drawing very definite conclusions. The addition of another thousand or five thousand specimens might easily result in marked changes in the ranking.

There is unfortunately no agreement as to how the "doubtful" results should be evaluated. The Evaluation Committee easily solved the difficulty by leaving them out altogether! A weakly positive report is frequently helpful in establishing a diagnosis of syphilis and the degree of alarm aroused by such a report in the non-syphilitic will vary with the judgment and experience of the clinician. But how is such a result to be evaluated in a table of percentages? If a test yields 1.1 per cent false positives and 1.1 per cent false doubtfuls, is it better or worse than one which gives 0.4 per cent false positives and 2.9 per cent false doubtfuls?

In attempting to interpret these reports it would seem more logical to utilize the information offered in the most flexible manner possible and to avoid making sharp and artificial distinctions such as between those which give less and those that give more than one per cent false positives. When one looks in this way at the tabulations and charts, one is impressed with the remarkable similarity of the results obtained with several technics and can note that from the standpoint of specificity there are five tests which group closely together. These are three flocculation tests, the Kline diagnostic test, the Kahn standard diagnostic test and the Weiss test, and two complement-fixation tests, those according to Kolmer and Brem. In the entire group only the Johns and the Lufkin and Rytz flocculation tests appear to be definitely out of line.

There is thus a wide choice of technics available for the serologic diagnosis of syphilis and it is not possible with certainty to select one of them as the best. The serologist is at liberty to choose any one of these methods of either flocculation or complement-fixation technic with the assurance that if he develops in his laboratory a high degree of technical excellence, he will have at

his command a test that will show a high degree of specificity of results and these results will probably be as good as those obtained in any other laboratory. Furthermore, and this should be especially emphasized, a flocculation test properly selected and properly performed, should show as great specificity as a complement-fixation test. The average clinician today still tends to regard the flocculation test with more or less suspicion. He is accustomed to call all serologic tests for syphilis "Wassermann tests," to believe the Wassermann technic to be highly reliable and to distrust the newer methods. The necessity for education in this field is obvious. The serologist partly in order to avoid this suspicion and partly to reinforce his results is very likely to carry out two tests on the specimens submitted to him and often selects one complement-fixation and one flocculation test. But a multiplication of methods cannot safely be carried very far and may result only in increased confusion. It is a striking fact that with the thirteen tests used in this survey, only about 60 per cent of the serums and 50 per cent of the spinal fluids furnished results that were in complete agreement. This figure would, of course, be larger if only the leading five tests were to be considered but nevertheless while the total percentage results may show remarkable agreement, it is found that the erroneous results do not involve the same specimens with each test. The serologist may, therefore, profitably and justifiably restrict himself to the use of two methods of high specificity.

There is much to be said, however, for the introduction of a test which shows a high degree of sensitivity and which is used as an "exclusion" test. In laboratories in which a large number of specimens are examined, there will be effected a marked saving in time and expense if all specimens are subjected to a highly sensitive test such as the Kline exclusion test (the Hinton test, though also very sensitive, is more time-consuming) and the more specific technics used only in those instances in which the sensitive test yields a doubtful or a positive result.

No consideration has been given in the official report to difficulty of technic or to time and expense required for the performance of the tests. On these counts there is much to be said

in favor of most of the flocculation tests and in these difficult times much more emphasis might justifiably be placed upon the fact that these methods employ a minimum number of reagents relatively stable and require a minimum of time for their execution.

One reform in reporting results has been advocated consistently by all conferences beginning with the first one in Copenhagen and that is the abandonment of the clumsy and arbitrary system of plus signs and the adoption of the simpler and probably more satisfactory nomenclature of "Negative," "Doubtful" and "Positive." Whether this would please those clinicians who are treating cases of syphilis is not known.

This conference very satisfactorily demonstrated the scarcity of the conditions in which falsely positive results may regularly be expected. Practically, these are restricted to leprosy and malaria. Leprosy is a purely academic question in this country and in the temperate zones generally and much further study is needed to determine whether the positive results in this disease are actually false. In malaria the percentage of false positives is not very large and these reactions do not persist after effective treatment of the malaria.

To summarize, the latest conference on serologic tests for syphilis shows that on the basis of both specificity and sensitivity the flocculation tests are equal or superior to the complement-fixation tests and that the best tests in both groups have reached a high degree of clinical specificity. The serologist may select any one of several available tests and still be assured of a reliable and satisfactory procedure. There is still necessary, however, a great deal of educational work before the average clinician will develop the ability to interpret properly the results of these tests. Development from now on should be along lines of standardization of reagents and technic, rather than of the introduction of new technics.

—Ralph G. Stillman.

NEWS AND NOTICES

Abstract of the Minutes of the Fifteenth Annual Convention of the American Society of Clinical Pathologists

Kansas City, Missouri

The business meeting was called to order by the President, Dr. R. A. Kilduffe at 8:15 p.m., June 10, 1936. The minutes of the previous meeting were approved as published in the official journal.

REPORT OF THE COMMITTEE ON CERTIFICATION OF PATHOLOGISTS

Dr. A. H. Sanford reported that through the efforts of the Committee for the Certification of Pathologists and a similar committee of the Section of Pathology of the American Medical Association, articles of incorporation and by-laws for the American Board of Pathology have been drawn up and accepted by the Advisory Board for Medical Specialties.

The Society accordingly voted to amend the by-laws of the constitution, as follows:

ARTICLE V

Add Section 7.

The Executive Committee shall appoint four representatives to serve on the Qualifying Board for Pathologists, in accordance with the stipulations of the By-laws of the American Board of Pathology.

The following men were selected by the Executive Committee: Dr. A. H. Sanford, Dr. F. H. Lamb, Dr. A. G. Foord, Dr. R. R. Kracke.

REPORT OF THE COMMITTEE ON CODE OF ETHICS

The Committee on Code of Ethics made their report and the recommendations were not accepted.

REPORT OF THE COMMITTEE ON SEMINARS

Dr. Lamb reported on the activities of the Seminar Committee and the Society voted to continue this Seminar as an integral part of the annual meeting.

REPORT OF THE COMMITTEE ON LIFE MEMBERSHIP

The Committee report was accepted and a recommendation made that the plans be incorporated in the by-laws of the Constitution in order that they may become more effective.

REPORT OF THE NECROLOGY COMMITTEE

Dr. G. B. Kramer reported the deaths of six members:

Dr. Foster M. Johns	New Orleans, Louisiana
Dr. Walter E. King	Grosse Point, Michigan
Dr. Walter G. Bain	Springfield, Illinois
Dr. Harry E. Braun	Houston, Texas
Dr. Charles Norris	New York, New York

The members rose in silent tribute to the deceased members.
The report was accepted.

REPORT OF THE COMMITTEE ON NECROPSIES

Dr. Davidsohn presented the report of the Committee. A bibliography for 1931 to 1934 was presented to the Secretary. During the past year the committee has been working on a similar bibliography for 1935, which will be submitted to the Secretary when completed.

The Committee has also been working on another problem: that is, the benefits to the family of the deceased by a post mortem examination.

The report was accepted.

After a recommendation by the Executive Committee, the Society voted to submit the collected bibliography on Necropsies presented by the Committee to the Editor for publication in the official journal.

REPORT OF THE PUBLIC RELATIONS COMMITTEE

The Committee recognizes three major problems confronting our Society:

(1) The tendency on the part of some public health laboratories to render services which are not of a strictly public health nature, and the danger of this being expanded in the future.

(2) The exploitation of the salaried pathologist in many hospitals, and the unfair competition of those hospital laboratories that bid for outside work at reduced fees.

(3) The teaching pathologist, who through a desire for increased income for himself or his department, offers services for tissue diagnosis, thereby depriving the practicing clinical pathologist of a field which is rightfully his.

The Committee reported on the study of the questionnaire on public health laboratories from replies received from thirty-eight states. It found that serologic tests for syphilis are done by state laboratories in all states, as well as examination of smears for gonorrhea, cultures for diphtheria and streptococci, aggutination test for typhoid, undulant fever, tularemia and typhus, sputum examination for tubercle bacilli, feces for amoeba and typhoid bacilli, blood cultures for typhoid bacilli and *Br. abortus*. In addition it was found that in twenty-one states the laboratory did urine and gastric analysis, in sixteen blood counts, in nine blood grouping, in seven complete spinal fluid examination, in eleven examination for rabies, and tissue diagnosis and water bacteriology, in nine blood chemistry and ten complete milk examinations. Of the thirty-eight states only eleven required that this service be limited to indigents although very little attempt is made to control abuse of this requirement. Seven of the states even offer home service, day or night. Many of these laboratories are not supervised by a pathologist. Seven states and the District of Columbia have laws controlling the operation of clinical laboratories.

The Committee suggested that a solution of this problem lay: (1), in a closer cooperation between the Society and the Surgeon General, who acts in an advisory capacity to the various state health departments. (2): That Pathologists in their respective territory should make a concerted action in arousing medical opinion to combat this first step in state medicine. Clinicians should be convinced of the fact that clinical pathology is a branch

of medicine and should be supported. A good example of such activity may be found by reading a recent editorial that appeared in the Colorado Medicine for November 1935. A copy of this may be obtained by writing to Dr. Philip Hillkowitz.

A survey of Hospital Laboratories is under way and a complete report will be made at the next annual meeting. From replies already received the Committee became aware of the fact that a large number of pathologists receive adequate compensation and enjoy their work. However, many hospitals are exploiting the pathologist and using the laboratory as a source of income to make up deficits of other departments.

The Committee recommended that the practice of hospital administrators who bid for outside work in competition with private practitioners of pathology should be discouraged and the cooperation of the American Medical Association and the American College of Surgeons be obtained in combating this abuse.

The problem of the teaching pathologist engaging in extramural practice of pathology could best be solved by encouraging physicians to use their influence to see that teaching pathologists receive adequate salary so that they need not be compelled to engage in clinical practice of pathology to the detriment of their teaching and research. It could be pointed out to them also that any teaching pathologists who are not licensed to practice medicine in their respective states are actually violating the medical practice act, since they render a diagnosis of tissue submitted to them.

(1) The Committee advised that the chairman of the Public Relations Committee be a member of the Executive Committee and hold office for three years, thus insuring more adequate cooperation between the Executive Committee and the Public Relations Committee on current problems.

(2) State or sectional organizations of clinical pathologists should be encouraged in order that they may study their local conditions and devise ways and means for correcting local abuses and improving the economic, as well as the scientific status of the clinical pathologists involved.

(3) The Committee recommends that the following broad principles be accepted by the Society.

a. Clinical pathology is a branch of the practice of medicine.

b. A clinical pathologist is entitled to an adequate income in proportion to his scientific ability and the volume of work which he does.

c. Any attempt on the part of hospital administrators to exploit the pathologist is to be condemned.

d. It shall be the constant aim of this Society to advance its members in scientific knowledge and to elevate them to further heights of influence with their fellow practitioners of medicine, so that their economic problems will be reduced to a minimum. The officers, the Executive Committee, and the Committee on Public Relations are empowered to further this aim in any way possible, consistent with the dignity of our specialty.

The report was accepted.

REPORT OF THE GENERAL RESEARCH COMMITTEE

The Committee reported on the progress on the various activities and many undertakings are being considered for the following year.

The reports were accepted.

REPORT OF THE SECRETARY-TREASURER

The officers and committees have been intensely busy with an unusual amount of business. The economic and political question of the time has reflected its share on the medical profession at large and to our Society in particular. The effect of the Wagner Bill legislation was carefully studied and appropriate action was taken by your president to protect our interests. The business of the Society was of such importance that the Executive Committee and officers convened in St. Louis, Missouri to transact it.

One of the outstanding contributions of the year has been the establishment of the pre-convention conference, so actively sponsored and developed by Dr. Lamb. The response to this

new activity has been unparalleled. The registration to this seminar totaled 113.

The total membership as of May 1, 1936 is 437. During the year of 1935–36 four members were reinstated to membership. Forty-eight members are in arrears for one year, six for two years, and one for three years. Five members are being dropped for non-payment of dues. Six members were lost because of death.

The financial report was approved by the Executive Committee; it showed a total income of $6046.26, total expenses of $4056.31 and a net income of $1389.95.

The report was accepted as read.

REPORT OF THE SERVICE BUREAU

During the past year the Service Bureau placed one applicant. The Committee urges members desiring to change positions to place their names on file. A motion was made to accept the report.

REPORT OF THE EXECUTIVE COMMITTEE

Dr. F. H. Lamb reported on the activities of the Executive Committee.

The Executive Committee has examined the records and financial report of the Secretary-Treasurer and found them to be in excellent condition. The Committee commented on the efficient and economic way in which the Society has been conducted.

The Committee has considered the activities of the Board of Registry and approved the financial statement. The Committee made the following recommendations to the Board of Registry:

a. That the Board should consult with the Executive Committee before embarking on any new policies.

b. That the approval of schools for laboratory technicians be turned over to the Council on Medical Education. The Board is to act in an advisory capacity.

c. That the single classification of registered technicians as "Medical Technologists" be adopted.

d. That the employment of registered technicians shall not be mandatory in those laboratories where there is adequate supervision of a competent clinical pathologist.

The Executive Committee approved the report of the journal and accepted with regrets the resignation of Dr. T. B. Magath as editor-in-chief and wish to express to him very deep appreciation for his efforts in bringing the official organ to its present position as one of the outstanding journals in the field of scientific publications. The Committee appointed Dr. R. A. Kilduffe as the succeeding editor-in-chief for 1937, 1938, and 1939.

The Executive Committee recommended that the by-laws of the constitution be amended by the addition of Section 7 to Article V.

The Committee presented a resumé of the activities in regard to the publication of a book on Approved Laboratory Technic and recommended that decision be left to the Society.

The report of the Executive Committee was accepted.

After due consideration the Society voted to withdraw its sponsorship or publication of a book on Approved Technic.

REPORT OF THE BOARD OF REGISTRY

Dr. Hillkowitz read the report of the Board of Registry. The present enrollment is 3164, of which 2112 are designated Laboratory Technicians and 1052 as Medical Technologists. Seven hundred and eighty-three new registrants were added to the roster in 1935–36.

The approval of training schools, another function of the registry, has shown a marked impetus this year. At present there are 85 approved schools. The burden of investigating schools has been shared by the Council on Medical Education. It is likely that the Council will assume its share of the responsibility of approval of schools for laboratory technicians.

The report was accepted.

ELECTION OF NEW MEMBERS

(This list was published in the July issue of the JOURNAL.)

NEW BUSINESS

A motion was made that the Society order the Secretary-Treasurer to prepare an appropriate medal to be given for meritorious service in clinical pathology to individuals appropriately chosen probably by a committee chosen by the President.

The motion was seconded and carried.

Dr. Lamb moved a vote of thanks to the local committee for their untiring efforts both before and during the meeting.

The motion carried unanimously.

REPORT OF THE NOMINATING COMMITTEE

(This was published in the July issue of the JOURNAL.)

APPOINTED COMMITTEES, 1936–37

Committee on Local Arrangements
S. P. Reimann, *Chairman*
Herbert Fox

Committee on Seminars
R. D'Aunoy, *Chairman*
H. M. Banks
E. L. Bishop
H. Fox
Philip B. Matz
E. von Haam

Committee on Annual Banquet
A. Yaguda, *Chairman*
W. G. Exton
R. A. Kilduffe
J. Eiman

Committee on Commercial Exhibits
A. W. Freshman, *Chairman*
A. S. Giordano
C. Y. White

Committee on Scientific Exhibits
E. von Haam, *Chairman*
F. P. Parker
F. W. Konzelmann

Program Committee
A. S. Giordano, *Chairman*
S. P. Reimann
F. J. Heck.

Committee on Life Membership
Oscar B. Hunter, *Chairman*
R. C. Beck

Committee on Necrology
H. C. Thornton, *Chairman*
G. S. Graham
H. S. Sumerlin

Committee on Necropsies
I. Davidsohn, *Chairman*
C. A. Hellwig
O. Saphir
M. Warwick

Publicity Committee
J. C. Norris, *Chairman*
M. P. Neal
C. J. Bucher

Committee on Public Relations
L. W. Larson, *Chairman*
F. O. Zillessen
C. I. Owen

Committee on Medal for Meritorious Work

H. C. Sweany, *Chairman*
A. S. Giordano
W. M. Simpson

Committee on General Research

A. M. Young, *Chairman*
General Committee:
F. W. Hartman
R. G. Stillman
Chemistry:
M. Bodansky
A. O. Gettler

Committee on General Research—Conc'd

Hormones:
H. L. Reinhart
A. M. Young
Bacteriology:
W. D. Stovall
F. W. Shaw
Serology:
B. S. Kline
Tumor Registry:
O. A. Brines
Hematology:
F. J. Heck
A. G. Foord
N. Rosenthal

Announcement is made that Doctor Harrison Martland has succeeded the late Doctor Charles Norris as Professor of Forensic Medicine in the New York University College of Medicine. The Charles Norris Fellowship in Forensic Medicine has been established.

Change in Editorship

With this issue of the Journal the Editorship of Doctor Thomas B. Magath comes to a close. He has served the first two, three year terms of the Journal. Doctor R. A. Kilduffe of Atlantic City, New Jersey, will assume the Editorship beginning with Volume 7. All communications and manuscripts should be sent to him.

THE AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS ROSTER FOR 1936

Officers

Dr. R. R. Kracke.....President
Dr. F. C. Narr.....Vice-President
Dr. C. W. Maynard.....President-Elect
Dr. Alfred S. Giordano.....Secretary-Treasurer

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Dr. F. H. Lamb, Chairman
Dr. L. W. Larson
Dr. A. G. Foord
Dr. K. Ikeda
Dr. W. M. Simpson
Dr. R. A. Kilduffe

Past Presidents

1922–3	Dr. Philip Hillkowitz	Denver, Colorado
1923–4	Dr. Wm. Carpenter MacCarty	Rochester, Minnesota
1924–5	Dr. John A. Kolmer	Bala-Cynwyd, Pa.
1925–6	Dr. Frederic E. Sondern	New York, N. Y.
1926–7	Dr. Wm. G. Exton	New York, N. Y.
1927–8	Dr. A. H. Sanford	Rochester, Minnesota
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1933–4	Dr. Alvin G. Foord	Pasadena, California
1934–5	Dr. Frederick H. Lamb	Davenport, Iowa
1935–6	Dr. Foster M. Johns	New Orleans, La.
1935–6	Dr. R. A. Kilduffe	Atlantic City, N. J.

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